Protocol I7P-MC-DSAD(a)

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3041658 in Adults with Moderate-to-Severe Hidradenitis Suppurativa

NCT04493502

Approval Date: 13-Aug-2021

Title Page

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3041658 in Adults with Moderate-to-Severe Hidradenitis Suppurativa

Protocol Number: I7P-MC-DSAD

Amendment Number: a

Compound: LY3041658

Study Phase: 2

Short Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3041658 in Adults with Moderate-to-Severe Hidradenitis Suppurativa

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Numbers

IND: 121924

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 13-Aug-2021 GMT

Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	13 March 2020

Amendment a

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

DSAD discontinuation rate has been higher than expected. The screening and enrollment numbers require increasing in order to reach the objective of the study.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Increased number of patients enrolled	Number of patients required increasing to ensure the objective of the study is met
Section 5.2 Exclusion Criteria	Exclusion Criterion 12, added HS wording Exclusion Criterion 16, the sites should use the 14 day/baseline (randomization) visit timing, not relative to the screening visit Exclusion Criterion 35, hemoglobin level corrected to 90.0 g/L	Clarification of prohibited concomitant therapy Clarification of prohibited concomitant therapy Error correction
Section 6.5.1 Washout Period Before Enrollment	Added HS wording	Clarification of prohibited concomitant therapy
Section 6.5.4 Prohibited Concomitant Therapy	Added HS wording	Clarification of prohibited concomitant therapy rules
Section 8.1.1.2 Modified Sartorius Score (mSS)	Lesion distance corrected	Error correction
Section 8.1.6 Patient's Global Impression of Severity – 7 Days (Hidradenitis Suppurativa)	Clarified scoring system	Changed to match Patient's Global Impression of Severity form

Section Number and Name	Description of Change	Brief Rationale
Section 8.1.8 Inflammatory Back Pain Assessment (ASAS Expert Criteria) and Spinal Pain Numeric Rating Scale (NRS)	Removed “at or” wording before the age of 40 years	To clarify that in reference it is <40 and not <=40
Section 9.2 Sample Size Determination	Number of patients enrolled increased	Number of patients required increasing to ensure the objective of the study is met
Section 10.3.4	Electronic data collection is not occurring Correction of SAE reporting	Correction Accuracy

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3041658 in Adults with Moderate-to-Severe Hidradenitis Suppurativa

Rationale: LY3041658 is a humanized immunoglobulin G (IgG) 4-variant monoclonal antibody (mAb) that binds to and neutralizes all 7 of the known ligands (referred to collectively as ELR+ [E = glutamic acid, L = leucine, R = arginine] chemokines) that signal through the human chemokine, CXC motif, receptors 1 and 2 (CXCR1 and CXCR2). LY3041658 binds to an epitope that is common to all 7 ELR+ chemokines. Signaling through CXCR1 and CXCR2 modulates neutrophil migration and angiogenesis, and neutrophil migration into sites of inflammation is critical to the pathogenesis of hidradenitis suppurativa (HS). Thus, LY3041658 is being developed for the treatment of HS. This proof-of-concept study will evaluate the safety and efficacy of LY3041658 in adults with HS.

Objectives and Endpoints

Objectives	Endpoints
Primary	
● To test the hypothesis that treatment with LY3041658 is superior to placebo in inducing Hidradenitis Suppurativa Clinical Response (HiSCR) in adult participants with moderate-to-severe hidradenitis suppurativa (HS)	● Proportion of participants achieving HiSCR response at Week 16
Secondary	
● To evaluate the efficacy of LY3041658 compared to placebo with respect to measures of signs and symptoms and pain in adult participants with moderate-to-severe HS	● Mean change from baseline to Week 16 in: ○ Total number of abscesses and inflammatory nodules (AN count) ○ Skin Pain – HS Numeric Rating Scale (NRS)

Note: HiSCR is defined as at least a 50% reduction in the total abscess and inflammatory nodule count (AN count) with no increase in abscess count and no increase in draining fistulae count relative to baseline.

Overall Design

Study I7P-MC-DSAD (DSAD) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 2 study to evaluate the efficacy and safety of LY3041658 600 mg given intravenously (IV) every 2 weeks (Q2W) in adults with HS.

The study duration will be up to approximately 51 weeks over 4 study periods:

Screening: a period lasting up to 35 days before Week 0 (Visit 2, baseline)

Treatment Period 1: a 16-week, 2-group double-blind treatment period

Treatment Period 2: a 20-week, single-group open-label extension period, and

Post-treatment follow-up: a period lasting approximately 10 weeks.

Topical antiseptics will be required as concomitant therapy during the study. Participants who were on stable doses of oral antibiotics at screening will remain on the same stable dose throughout the study.

Disclosure Statement: In this study, the 2-arm parallel treatment period is participant-blinded and investigator-blinded and is followed by a single-arm open-label extension treatment period.

Number of Participants: Approximately 100 patients will be screened to achieve approximately 63 randomized participants.

Intervention Groups and Duration:

At baseline, participants will be randomized in a 2:1 ratio to one of two treatments groups:

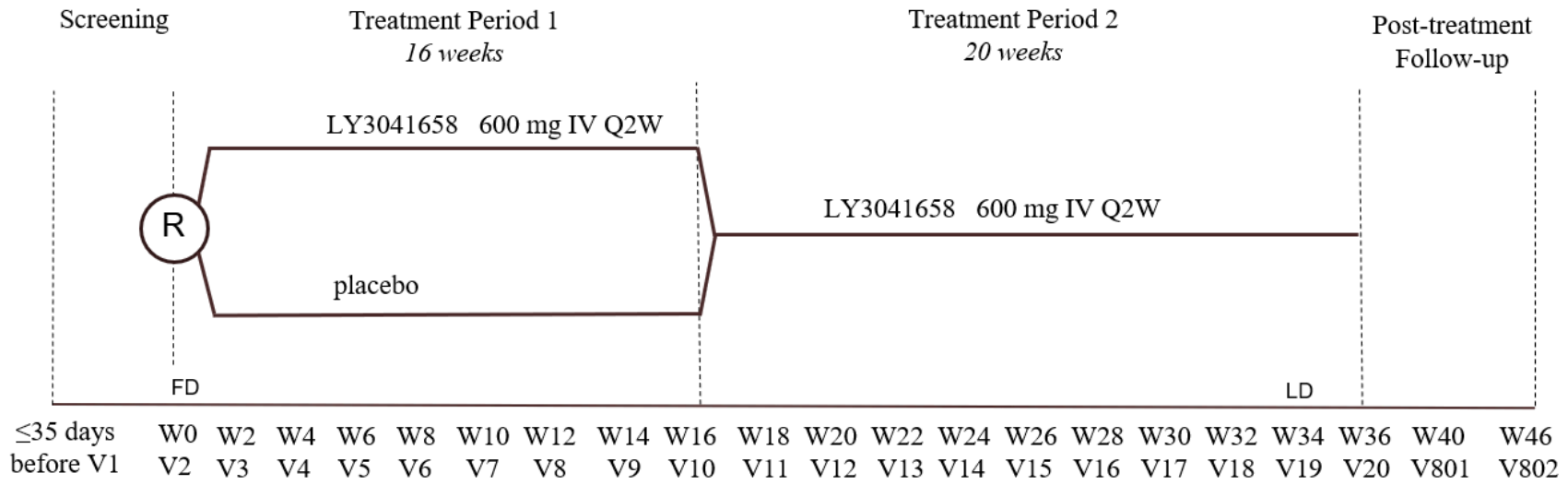
Approximately 42 participants will receive LY3041658 600 mg IV Q2W for 16 weeks, and

Approximately 21 participants will receive placebo IV Q2W for 16 weeks.

Starting at Week 16, all participants, including those previously assigned to placebo, will receive LY3041658 600 mg IV Q2W for 20 weeks.

Data Monitoring Committee: No

1.2. Schema



Note: Starting at Week 16 participants who received placebo in Treatment Period 1 will receive LY3041658 600 mg IV Q2W.

Abbreviations: FD = first dose; IV = intravenous; LD = last dose; Q2W = every 2 weeks; R = randomization visit; V = visit; W = study week relative to randomization visit.

Figure 1. Schema of Study I7P-MC-DSAD, a Phase 2 study to evaluate the efficacy and safety of LY3041658 in adults with moderate-to-severe hidradenitis suppurativa.

1.3. Schedule of Activities (SoA)

Table 1. Schedule of activities for the Screening Period and Treatment Period 1 of Study I7P-MC-DSAD

Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance.
For procedures at an early termination visit, see ETV in Table 2.
For procedures at an unscheduled visit, see V997 in Table 2. Unscheduled visits are for participants needing rescue therapy or incision and drainage.

Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**Comment**
Weeks from randomization	–5	—	2	4	6	8	10	12	14	16	
Study day	—	1	15	29	43	57	71	85	99	113	
Visit interval tolerance (days)	≤35	—	±2	±2	±2	±2	±2	±2	±2	±2	
Fasting visit		**X**								**X**	
Informed consent	X										
Inclusion and exclusion criteria, review and confirm	X	X									
Demographics	X										
Preexisting conditions and medical history	X										
Prespecified medical history (indication and history of interest)	X										
Prior treatments for indication	X										Relevant surgical history
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	For AESIs, additional data are collected (Section 8.3.6).
Substance use (alcohol, caffeine, tobacco)	X										
Surgical interventions related to HS		X	X	X	X	X	X	X	X	X	
Physical Evaluation											
Height	X										Without shoes.
Weight	X									X	
Vital signs	X	X	X	X	X	X	X	X	X	X	Blood pressure, body temperature, pulse rate. Vital signs should be measured after participant has been sitting for at least 5 minutes.

Table 1. Schedule of activities for the Screening Period and Treatment Period 1 of Study I7P-MC-DSAD

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Weeks from randomization	–5	—	2	4	6	8	10	12	14	16	
Study day	—	1	15	29	43	57	71	85	99	113	
Visit interval tolerance (days)	≤35	—	±2	±2	±2	±2	±2	±2	±2	±2	
Fasting visit		**X**								**X**	
Physical examination	X										The complete physical exam will exclude pelvic, rectal, and breast exams and will include assessment for signs and symptoms of tuberculosis (TB), including peripheral lymph nodes (Section 8.2.2).
Symptom-directed physical examination		X	X	X	X	X	X	X	X	X	See Section 8.2.2.
12-lead ECG (local)	X									X	
Chest x-ray (posterior-anterior view) (local)	X										Interpreted and reported by radiologist or pulmonologist. Not performed at screening if performed within 6 months before screening and if qualifying radiographs or equivalent imaging study and/or formal report are available for investigator's review and sufficient for TB evaluation according to local standard of care (Section 8.2.4).
Patient-Reported Outcomes (Electronic)											
DLQI		X		X		X		X		X	
Skin Pain – HS NRS		X	X	X	X	X	X	X	X	X	
Drainage NRS		X	X	X	X	X	X	X	X	X	
Smell NRS		X	X	X	X	X	X	X	X	X	
Patient's Global Impression of Severity – 7 Days (Hidradenitis Suppurativa)		X	X	X	X	X	X	X	X	X	
Patient Global Impression of Change – 7 Days (Hidradenitis Suppurativa)		X						X		X	

Table 1. Schedule of activities for the Screening Period and Treatment Period 1 of Study I7P-MC-DSAD

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Weeks from randomization	–5	—	2	4	6	8	10	12	14	16	
Study day	—	1	15	29	43	57	71	85	99	113	
Visit interval tolerance (days)	≤35	—	±2	±2	±2	±2	±2	±2	±2	±2	
Fasting visit		**X**								**X**	
Patient-Reported Outcomes (Paper)											
Spinal Pain NRS		X								X	See Section 8.1.8.
Clinician-Administered Questionnaires (Electronic)											
Lesion assessments	X	X	X	X	X	X	X	X	X	X	Includes anatomical region, type and number (see Section 8.1.1).
Hurley stage	X	X									
Clinician-Administered Questionnaires (Paper)											
C-SSRS Screening/Baseline	X										
C-SSRS Since Last Visit		X	X	X	X	X	X	X	X	X	
Self-Harm Supplement Form	X	X	X	X	X	X	X	X	X	X	
Self-Harm Follow-Up Form	X	X	X	X	X	X	X	X	X	X	Required if triggered by the Self-Harm Supplement Form per instructions.
Inflammatory Back Pain Assessment (ASAS Expert Criteria)		X									See Section 8.1.8.
Laboratory Tests and Sample Collections											
Hematology	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	
Lipid panel		X								X	Participants should not eat or drink anything but water for 12 hours before the visit. Fasting is not required at an ETV. If a participant attends these visits in a nonfasting state, the sample should still be collected. This will not be considered a protocol violation.
Urinalysis	X	X								X	

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Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**Comment**
Weeks from randomization	–5	—	2	4	6	8	10	12	14	16	
Study day	—	1	15	29	43	57	71	85	99	113	
Visit interval tolerance (days)	≤35	—	±2	±2	±2	±2	±2	±2	±2	±2	
Fasting visit		**X**								**X**	
Serum pregnancy	X										Only for WOCBP (Section 8.2.5.1, Appendix 10.4) and women with a history of tubal ligation. Central laboratory.
Urine pregnancy (local)		X	X	X	X	X	X	X	X	X	Only for WOCBP (Section 8.2.5.1, Appendix 10.4) and women with a history of tubal ligation. Result must be negative before dosing at each dosing visit.
Follicle-stimulating hormone (FSH)	X										Optional, performed to confirm postmenopausal status (Section 8.2.5.1)
Tuberculosis (TB) test	X										Patients who had a tuberculin skin test (TST) will return from 48 to 72 hours after placement to have their test results read (Section 8.2.6). Samples may be sent to a central or local laboratory based on the type of test. A local laboratory must be qualified by local regulations.
HIV screening tests	X										
Hepatitis C virus (HCV) screening tests	X										HCV RNA will be measured to confirm positive hepatitis C virus antibody (Section 8.2.8).
Hepatitis B virus (HBV) screening tests	X										Includes testing for HBsAg and anti-HBc (Section 8.2.7)
C-reactive protein, high-sensitivity (hs-CRP)		X		X				X		X	
IL-8		X	X			X				X	
Total immunoglobulins (IgA, IgE, IgG, and IgM)		X								X	If a hypersensitivity event occurs, collect additional samples (see Appendix 10.2, Section 10.2.2).

Table 1. Schedule of activities for the Screening Period and Treatment Period 1 of Study I7P-MC-DSAD

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For procedures at an unscheduled visit, see V997 in Table 2. Unscheduled visits are for participants needing rescue therapy or incision and drainage.

Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**Comment**
Weeks from randomization	–5	—	2	4	6	8	10	12	14	16	
Study day	—	1	15	29	43	57	71	85	99	113	
Visit interval tolerance (days)	≤35	—	±2	±2	±2	±2	±2	±2	±2	±2	
Fasting visit		**X**								**X**	
Pharmacokinetic (PK) sample		X	X	X		X		X		X	At Visit 2, Visit 10, and Visit 19, collect samples at 3 time points: [redacted] If a hypersensitivity event occurs, collect additional samples (see (Appendix 10.2, Section 10.2.2).
Immunogenicity (ADA) sample		X		X						X	Collect samples before dosing, if dosing is scheduled. If a hypersensitivity event occurs, collect additional samples (see Appendix 10.2, Section 10.2.2). See Section 8.9 for additional details.
Exploratory biomarker sample – Whole blood for RNA and for epigenetics,		X		X						X	
Pharmacogenetics sample (DNA)	X										
Exploratory biomarker samples - other		X	X	X		X		X		X	At Visit 2 and Visit 10, collect samples before the infusion starts.
Randomization and dosing											
Randomization		X									
Dosing		X	X	X	X	X	X	X	X	X	No dosing at Visit 1, Visit 20, ETV, or V997.

Abbreviations: ADA = anti-drug antibody; AESI = adverse event of special interest; anti-HBc = antibody to hepatitis B core antigen; ASAS = Assessment of SpondyloArthritis International Society; C-SSRS = Columbia Suicide-Severity Rating Scale; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ETV = early termination visit; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; HS = hidradenitis suppurativa; NRS = numeric rating scale; RNA = ribonucleic acid; V = visit; WOCBP = women of childbearing potential.

Table 2. Schedule of activities for Treatment Period 2 of Study I7P-MC-DSAD

For procedures at an early termination visit, see ETV in Table 2.

For procedures at an unscheduled visit, see V997 in Table 2. Unscheduled visits are for participants needing rescue therapy or incision and drainage.

Visit number	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	ETV	V997	Comment
Week from randomization	18	20	22	24	26	28	30	32	34	36	—	—	
Study day	127	141	155	169	183	197	211	225	239	253	—	—	
Visit interval tolerance (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	—	—	
Fasting visit										**X**			
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	For AESIs, additional data are collected (Section 8.3.6).
Surgical interventions related to HS	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Evaluation													
Weight										X	X		
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	Blood pressure, body temperature, pulse rate. Vital signs should be measured after participant has been sitting for at least 5 minutes.
Symptom-directed physical examination	X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.2.2.
12-lead ECG (local)										X	X		
Patient-Reported Outcomes (Electronic)													
DLQI				X				X		X	X		
Skin Pain – HS NRS		X		X		X		X		X	X	X	
Drainage NRS		X		X		X		X		X	X	X	
Smell NRS		X		X		X		X		X	X	X	
Patient's Global Impression of Severity – 7 Days (Hidradenitis Suppurativa)		X		X		X		X		X	X	X	

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For procedures at an early termination visit, see ETV in Table 2.

For procedures at an unscheduled visit, see V997 in Table 2. Unscheduled visits are for participants needing rescue therapy or incision and drainage.

Visit number	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	ETV	V997	Comment
Week from randomization	18	20	22	24	26	28	30	32	34	36	—	—	
Study day	127	141	155	169	183	197	211	225	239	253	—	—	
Visit interval tolerance (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	—	—	
Fasting visit										**X**			
Patient Global Impression of Change – 7 Days (Hidradenitis Suppurativa)										X	X	X	
Patient-Reported Outcomes (Paper)													
Spinal Pain NRS										X	X	X	See Section 8.1.8.
Clinician-Administered Questionnaires (Electronic)													
Lesion assessments	X	X	X	X	X	X	X	X	X	X	X	X	Includes anatomical region, type and number (see Section 8.1.1).
Clinician-Administered Questionnaires (Paper)													
C-SSRS Since Last Visit	X	X	X	X	X	X	X	X	X	X	X	X	
Self-Harm Supplement Form	X	X	X	X	X	X	X	X	X	X	X	X	
Self-Harm Follow-Up Form	X	X	X	X	X	X	X	X	X	X	X	X	Required if triggered by the Self-Harm Supplement Form per instructions.
Laboratory Tests and Sample Collections													
Hematology	X	X	X	X	X	X	X	X	X	X	X		
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X		

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For procedures at an early termination visit, see ETV in Table 2.

For procedures at an unscheduled visit, see V997 in Table 2. Unscheduled visits are for participants needing rescue therapy or incision and drainage.

Visit number	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	ETV	V997	Comment
Week from randomization	18	20	22	24	26	28	30	32	34	36	—	—	
Study day	127	141	155	169	183	197	211	225	239	253	—	—	
Visit interval tolerance (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	—	—	
Fasting visit										**X**			
Lipid panel										X	X		Participants should not eat or drink anything but water for 12 hours before the visit. Fasting is not required at an ETV. If a participant attends these visits in a nonfasting state, the sample should still be collected. This will not be considered a protocol violation.
Urinalysis										X	X		
Urine pregnancy (local)	X	X	X	X	X	X	X	X	X	X	X		Only for WOCBP (Section 8.2.5.1, Appendix 10.4) and women with a history of tubal ligation. Result must be negative before dosing at each dosing visit.
C-reactive protein, high-sensitivity (hs-CRP)										X	X		
IL-8	X				X					X	X		
Total immunoglobulins (IgA, IgE, IgG, and IgM)										X	X		If a hypersensitivity event occurs, collect additional samples (see Appendix 10.2, Section 10.2.2).

Table 2. Schedule of activities for Treatment Period 2 of Study I7P-MC-DSAD

For procedures at an early termination visit, see ETV in Table 2.

For procedures at an unscheduled visit, see V997 in Table 2. Unscheduled visits are for participants needing rescue therapy or incision and drainage.

Visit number	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	ETV	V997	Comment
Week from randomization	18	20	22	24	26	28	30	32	34	36	—	—	
Study day	127	141	155	169	183	197	211	225	239	253	—	—	
Visit interval tolerance (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	—	—	
Fasting visit										**X**			
Pharmacokinetic (PK) sample	X	X			X			X	X	X	X		At Visit 2, Visit 10, and Visit 19, collect samples at 3 time points:  If a hypersensitivity event occurs, collect additional samples (see (Appendix 10.2, Section 10.2.2).
Immunogenicity (ADA) sample		X			X			X		X	X		Collect samples before dosing, if dosing is scheduled. If a hypersensitivity event occurs, collect additional samples (see Appendix 10.2, Section 10.2.2). See Section 8.9 for additional details.
Exploratory biomarker samples - other		X			X			X		X	X		
Dosing													
Dosing	X	X	X	X	X	X	X	X	X				No dosing at Visit 1, Visit 20, ETV, or V997.

Abbreviations: ADA = anti-drug antibody; AESI = adverse event of special interest; C-SSRS = Columbia Suicide-Severity Rating Scale; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; ETV = early termination visit; HS = hidradenitis suppurativa; NRS = numeric rating scale; V = visit; WOCBP = women of childbearing potential.

Table 3. Schedule of activities for the Post-Treatment Follow-Up Period of Study I7P-MC-DSAD

For procedures at an early termination visit, see ETV in Table 2.

For procedures at an unscheduled visit, see V997 in Table 2. Unscheduled visits are only for participants needing rescue therapy or incision and drainage.

Visit number	**V801**	**V802**	**Comment**
Week relative to randomization	40 or ETV+4	46 or ETV+10	
Study day	281	323	
Visit interval tolerance (days)	±7	±7	
Fasting visit			No fasting in this period.
Concomitant medications	X	X	
Adverse events	X	X	For AESIs, additional data are collected (Section 8.3.6).
Surgical interventions related to HS	X	X	
Physical Evaluation			
Vital signs	X	X	Blood pressure, body temperature, pulse rate. Vital signs should be measured after participant has been sitting for at least 5 minutes.
Symptom-directed physical examination	X	X	See Section 8.2.2.
Patient-Reported Outcomes (Electronic)			
Skin Pain – HS NRS	X	X	
Drainage NRS	X	X	
Smell NRS	X	X	
Patient's Global Impression of Severity – 7 Days (Hidradenitis Suppurativa)	X	X	
Patient-Reported Outcomes (Paper)			
Spinal Pain NRS	X	X	See Section 8.1.8.
Clinician-Administered Questionnaires (Electronic)			
Lesion assessments	X	X	Includes anatomical region, type and number (see Section 8.1.1).
Clinician-Administered Questionnaires (Paper)			
C-SSRS Since Last Visit	X	X	
Self-Harm Supplement Form	X	X	
Self-Harm Follow-Up Form	X	X	Required if triggered by the Self-Harm Supplement Form per instructions.
Laboratory Tests and Sample Collections			
Hematology	X	X	
Clinical chemistry	X	X	

Table 3. Schedule of activities for the Post-Treatment Follow-Up Period of Study I7P-MC-DSAD

For procedures at an early termination visit, see ETV in Table 2.

For procedures at an unscheduled visit, see V997 in Table 2. Unscheduled visits are only for participants needing rescue therapy or incision and drainage.

Visit number	V801	V802	Comment
Week relative to randomization	40 or ETV+4	46 or ETV+10	
Study day	281	323	
Visit interval tolerance (days)	±7	±7	
Fasting visit			No fasting in this period.
Urine pregnancy (local)	X	X	Only for WOCBP (Section 8.2.5.1 and Appendix 10.4) and women with a history of tubal ligation.
C-reactive protein, high-sensitivity (hs-CRP)		X	
Pharmacokinetic (PK) sample	X	X	If a hypersensitivity event occurs, collect additional samples (see Appendix 10.2, Section 10.2.2).
Immunogenicity (ADA) sample		X	If a hypersensitivity event occurs, collect additional samples (see Appendix 10.2, Section 10.2.2). See Section 8.9 for additional details.
Dosing			No dosing in this period

Abbreviations: ADA = anti-drug antibody; AESI = adverse event of special interest; C-SSRS = Columbia Suicide-Severity Rating Scale; ETV = early termination visit; HS = hidradenitis suppurativa; NRS = numeric rating scale; V = visit; WOCBP = women of childbearing potential.

2. Introduction

2.1. Study Rationale

LY3041658 is a humanized immunoglobulin G (IgG) 4-variant monoclonal antibody (mAb) that binds to and neutralizes all 7 of the known ligands (referred to collectively as ELR+ [E = glutamic acid, L = leucine, R = arginine] chemokines) that signal through the human chemokine, CXC motif, receptors 1 and 2 (CXCR1 and CXCR2). LY3041658 binds to an epitope that is common to all 7 ELR+ chemokines. Signaling through CXCR1 and CXCR2 modulates neutrophil migration and angiogenesis, and neutrophil migration into sites of inflammation is critical to the pathogenesis of hidradenitis suppurativa (HS). Thus, LY3041658 is being developed for the treatment of HS.

Study I7P-MC-DSAD (DSAD) is a Phase 2 study to evaluate the safety and efficacy of LY3041658 in adult patients with HS. Results of this study will provide information useful to guiding dose selection in future studies and to further characterize the benefit/risk profile of LY3041658.

2.2. Background

Hidradenitis suppurativa (HS) or acne inversa is a chronic, recurrent, inflammatory, debilitating skin disease usually presenting after puberty with painful, deep, inflamed lesions in the apocrine gland-bearing areas of the body, commonly the inguinal axillaries, and anogenital regions (Zouboulis et al. 2015; Zouboulis 2006).

Even when HS lesions heal, permanent fibrosis, dermal contractures, and induration of the skin frequently occur. These tissue changes can be physically, psychologically, and cosmetically debilitating. As tissue damage accumulates over time, patients frequently develop low self-esteem and loneliness (Kouris et al. 2016) and become socially withdrawn, unable to maintain employment, and susceptible to poverty, depression, and suicidality (Vekic and Cains 2017).

There is currently no uniformly effective single therapy for HS. Numerous treatment modalities are employed, including antibiotics, retinoids, hormones, immunosuppressive and anti-inflammatory agents, neurotoxins, radiotherapy, and surgery. The tumor necrosis factor inhibitor adalimumab has been approved in the United States, Europe, and Australia for the treatment of moderate-to-severe HS (Zouboulis et al. 2015; Kimball et al. 2016a; Vekic and Cains 2017). Yet substantial unmet medical needs remain, since adalimumab fails either to treat many patients adequately or to maintain treatment effect over time (Kimball et al. 2016a). Patients with HS are appropriate for a novel investigational product (IP) with immunomodulating properties.

2.3. Benefit/Risk Assessment

The efficacy of LY3041658 in HS has not been established. However, LY3041658 decreased neutrophil migration into cantharidin-induced blisters in healthy participants (data on file, Study I7P-MC-DSAA [DSAA]). These findings support the hypothesis that LY3041658 has the

potential for efficacy in HS and other neutrophilic skin diseases. Furthermore, participants may benefit by receiving personal health information from the physical examinations and from other routine safety assessments performed in this study.

At this time, there are no known adverse drug reactions (ADRs) or known risks considered to be associated with LY3041658. No dose-limiting events were observed in the Phase 1 studies DSAA and I7P-MC-DSAB [DSAB].

In the Phase 1 Study DSAA, single doses of up to 700 mg of LY3041658 administered to healthy study participants were generally well tolerated with the exception of a mild, short-lived, infusion-associated reaction in 1 participant in a 700-mg cohort.

In the Phase 1 Study DSAB, participants with psoriasis, HS, or palmoplantar pustulosis received 40 mg to 600 mg doses of LY3041658 every 2 weeks. The most common treatment-emergent adverse events were infections such as cellulitis, sinusitis and respiratory tract infections. Most adverse events were mild to moderate (CTCAE Grade 1 or Grade 2) severity. There was one severe event of elevated gamma-glutamyl transferase (GGT) (CTCAE Grade 3); this event in a single participant assigned to LY3041658 300 mg, and it was not accompanied by symptoms or changes in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 times the upper limit of normal (ULN).

To minimize participant risk in Study DSAD, all participants will be monitored closely after completion of each intravenous (IV) infusion (Section 6.1). In addition, all participants will undergo regular monitoring of routine laboratory safety tests (clinical chemistry, hematology, and urinalysis). Monitoring of safety data will be performed on an ongoing basis, as described in Section 8.2. Interim analyses to review unblinded safety data will also be conducted, as described in Section 9.5 and Appendix 10.1, Section 10.1.5.

In summary, in the context of the cumulative knowledge for LY3041658, the benefit/risk balance for this study is assessed to be favorable.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of LY3041658 may be found in the Investigator's Brochure (IB).

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
● To test the hypothesis that treatment with LY3041658 is superior to placebo in inducing Hidradenitis Suppurativa Clinical Response (HiSCR) in adult participants with moderate-to-severe hidradenitis suppurativa (HS)	● Proportion of participants achieving HiSCR response at Week 16
Secondary	
● To evaluate the efficacy of LY3041658 compared to placebo with respect to measures of signs and symptoms and pain in adult participants with moderate-to-severe HS	● Mean change from baseline to Week 16 in: ○ Total number of abscesses and inflammatory nodules (AN count) ○ Skin Pain – HS Numeric Rating Scale (NRS)
Exploratory	
Exploratory objectives and endpoints may include the following: ● To evaluate, at various time points, the efficacy of LY3041658 compared to placebo in inducing improvements in signs and symptoms and quality of life ● To characterize the pharmacokinetics (PK) of LY3041658 and to explore relationships between LY3041658 exposure and select biomarkers and clinical efficacy endpoints ● To assess the potential development of anti-LY3041658 antibodies and their impact on the safety profile and PK of LY3041658	

Note: HiSCR is defined as at least a 50% reduction in the total abscess and inflammatory nodule count (AN count) with no increase in abscess count and no increase in draining fistulae count relative to baseline.

4. Study Design

4.1. Overall Design

Study I7P-MC-DSAD (DSAD) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 2 study to evaluate the efficacy and safety of LY3041658 600 mg given intravenously (IV) every 2 weeks (Q2W) in adults with HS.

The study duration will be up to approximately 51 weeks over 4 study periods:

Screening: a period lasting up to 35 days before Week 0 (Visit 2, baseline)

Treatment Period 1: a 16-week, 2-group double-blind treatment period:

- At baseline (Visit 2, Week 0), eligible participants will be randomized in a 2:1 ratio to receive either LY3041658 600 mg IV Q2W or placebo IV Q2W, starting at the baseline visit.

Treatment Period 2: a 20-week, single-group open-label extension period:

- Starting at Week 16, all participants, including those previously assigned to placebo, will receive LY3041658 600 mg IV Q2W until the last dosing visit.

Post-treatment follow-up: a period lasting approximately 10 weeks.

- Participants will not receive study drug in this period.
- The last dose of study drug is given at Visit 19 (Week 34). Thus, participants will have been withdrawn from study drug for a total of 12 weeks at the last post-treatment follow-up visit (Visit 802, Week 46).

The study schema is presented in Section 1.2.

Unscheduled visits are for participants needing rescue therapy or incision and drainage. The use of concomitant medications, including rescue therapy, is described in Section 6.5.

Participants who permanently discontinue the study drug early (Section 7.1) will undergo early termination procedures, including an early termination visit (ETV) and the post-treatment follow-up visits specified in the Schedule of Activities (SoA) (Section 1.3).

4.2. Scientific Rationale for Study Design

The primary endpoint of this study is the proportion of patients achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 16. HiSCR is defined as at least a 50% reduction in the total abscess and inflammatory nodule count (AN count) with no increase in abscess count and no increase in draining fistulae count relative to baseline. HiSCR has been used in previous HS trials and has been accepted by the Food and Drug Administration as a primary endpoint (Kimball et al. 2014; Kimball et al. 2016a; Kimball et al. 2016b). Evaluation of the primary endpoint at the Week 16 time point is appropriate based on current clinical trials of systemic immunomodulatory therapies in HS (guselkumab NCT03628924, secukinumab NCT03713632 and NCT03713619; bimekizumab NCT04242498 and NCT04242446).

A double-blind, placebo-controlled design through the first treatment period limits bias for the participant and investigator assessments and enables a clearer interpretation of the effects of active drug.

The second treatment period (open-label) allows for evaluation of both safety and changes in efficacy over time in participants who received LY3041658 in the placebo-controlled treatment period. The second treatment period also allows participants who were randomized to placebo in the first treatment period to receive LY3041658 in the open-label period for a treatment duration similar to that of the placebo-controlled period.

The post-treatment follow-up period allows for continued safety monitoring after the last dose. The last dose is given at Week 34. This is 2 weeks before the last visit in the second treatment period (Week 36) and a total of 12 weeks before the last post-treatment follow-up visit (Week 46). LY3041658 concentrations are expected to be significantly decreased in the plasma after 5 half-lives. The terminal half-life of LY3041658 is approximately 2 weeks, based on pharmacokinetic (PK) data from the Phase 1 Study DSAB. Therefore, for the present study, the planned duration of safety follow-up is adequate, as this duration covers approximately 6 half-lives. A follow-up period of a similar duration was used after the last dose of LY3041658 in the single-dose Study DSAA and multiple-dose Study DSAB.

4.2.1. Participant Input into Design

The sponsor involved patients in the design of this study by engaging patients in simulations and other face-to-face or virtual collaborative events for related HS trials. The insights gained from these events were used to ensure that this study design is supportive of the well-being of the study participants and that the study procedures can be implemented effectively at the investigative sites.

4.3. Justification for Dose

The dose of 600 mg IV Q2W matches the highest dose administered in the multiple-dose Study DSAB. The Q2W dosing frequency was selected because the LY3041658 terminal half-life is approximately 2 weeks. In Study DSAB, three participants with HS received 4 doses of LY3041658 Q2W. There were no deaths, serious adverse events, or treatment-emergent adverse events leading to discontinuation in Study DSAB.

Exploratory modeling of neutrophil migration into cantharidin-induced blisters in healthy participants (Study DSAA) was performed. Although the neutrophil data was highly variable, a trend of dose-dependent decreases of neutrophils in the blister fluid was observed. Based on simulations using the exploratory PK/PD model, a 600 mg IV Q2W dose was predicted to reduce neutrophil migration to <20% of the baseline value.

The margin of safety (MOS) calculation is summarized in the IB. The estimated AUC(0-168) exposure based on three HS participants at the clinical IV dose of 600 mg (71500 µg*hr/mL) in humans is 7.2-fold lower than the AUC(0-168) at the NOAEL (125 mg/kg IV) in cynomolgus monkeys administered LY3041658 once weekly for 6 months.

See the IB for additional information.

4.4. End-of-Study Definition

A participant is considered to have completed the study if he or she has completed all required phases of the study, including the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

The “end of the study” is defined as the date of the last visit or last scheduled procedure shown in the SoA for the last participant in the study globally.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

For screen failures and rescreening activities within the screening period, see Section 5.4.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if they meet all of the following criteria during the screening period, unless otherwise specified below:

Informed consent

[1] Are capable of giving signed informed consent as described in Appendix 10.1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Participant characteristics

[2] Are male or female patients from 18 to 65 years of age (inclusive), at the time of signing the ICF.

Note: Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Contraception requirements for participants in this study are provided in Appendix 10.4.

HS-related inclusion criteria

[3] Have a diagnosis of HS for at least 6 months before baseline (the randomization visit).

Note: a participant with a clinical history of HS may be considered for enrollment if other eligibility criteria are met and if the clinical history is documented by the investigator based on review of the participant's medical history at screening.

[4] Have HS lesions in at least 2 distinct anatomical regions (for example, right and left axilla; or right axilla and right inguino-crural fold); and at least one of the lesions must be at least Hurley Stage II or Hurley Stage III.

[5] Have had an inadequate response or intolerance to a 28-day course of oral antibiotics. Examples of inadequate response include the following: any lesion increased in Hurley stage, any lesion requiring intra-lesional steroid injection or incision and drainage, and/or any new anatomic areas developed lesions during the antibiotic course.

[6] Have a total abscess and inflammatory nodule (AN) count greater than or equal to 4.

[7] Must agree to use daily, and throughout the duration of the study, one of the following over-the-counter topical antiseptics on body areas affected with HS lesions: chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in water.

[8] Are able and willing to comply with the following requirements for use of antibiotics:

If using topical antibiotics for HS at screening, the participant must stop them at least 14 days before baseline (the randomization visit) and must not resume topical antibiotics throughout the duration of the study.

If using oral antibiotics for HS at screening and intends to continue them during the study, the participant must have been on a stable dose for at least 4 weeks before screening and must remain on the same stable dose throughout the duration of the study.

If using oral antibiotics for HS at screening and intends not to take them during the study, the participant must have stopped using them at least 14 days before the planned randomization visit (see Section 6.5).

Note: Participants may be considered for enrollment if they have received oral antibiotics for HS prior to screening but have stopped that use at least 14 days before the planned randomization visit.

5.2. Exclusion Criteria

Participants will be excluded from study enrollment if they meet any of the following criteria within the screening period, unless otherwise specified:

Skin diseases and conditions

[9] Have more than 20 draining fistulae.

[10] Have had surgical treatment for HS in the last 4 weeks prior to baseline (the randomization visit).

[11] Have active skin disease or condition (for example, bacterial, fungal or viral infection) that could interfere with assessment of HS.

Prior or concomitant therapy

[12] Are unwilling or unable to stop treatment with topical antibiotics for HS 14 days prior to baseline (the randomization visit) and for the duration of the study.

[13] Have received any biologic agent for treatment of HS (for example, adalimumab) at any time.

[14] Have received any biologic agent (such as monoclonal antibodies, whether investigational or marketed) for any indication other than HS within 3 months or 5 half-lives (whichever is longer) before baseline (the randomization visit).

Note: Participants may be considered for enrollment if they have stopped receiving a biologic agent for an indication other than HS at least 3 months or 5 half-lives (whichever is longer) before baseline (the randomization visit) and if all other eligibility criteria are met.

[15] Have received any systemic nonbiologic immunosuppressive medication for any indication within 28 days before baseline (the randomization visit).

[16] Have received oral opioids for HS-related pain within 14 days before baseline (the randomization visit) or are anticipated to receive oral opioids for HS-related pain during the study.

Note: Participants may be considered for enrollment if they have stopped receiving oral opioids for HS-related pain more than 14 days before the baseline visit and if all other eligibility criteria are met.

[17] Have received any systemic (including oral) antibiotic or anti-infective treatment within 28 days prior to baseline (the randomization visit), unless as required for latent tuberculosis infection (LTBI) treatment (see criterion #25) or prescribed for HS (see criterion #8).

[18] Have a history of chronic alcohol abuse, IV drug abuse, or other illicit drug abuse within 1 year prior to the screening visit.

Note: Marijuana is considered an illicit drug for the purposes of this study, regardless of local laws. Cannabidiol (CBD) products may be used during the study if they are derived exclusively from hemp. Participants who use hemp-based CBD products must be on a stable dose for at least 14 days prior to baseline (the randomization visit), and participants must remain on that stable dose during the study.

Current or historical infections

[19] Have a current or recent acute, active infection. For at least 30 days prior to screening and up to the randomization visit, participants must have no symptoms or signs of confirmed or suspected infection, and must have completed any appropriate anti-infective treatment.

Note: Participants with an active upper respiratory infection that is being treated only symptomatically and does not require anti-infectives may be considered for enrollment if other eligibility criteria are met.

[20] Have had, within 12 weeks of screening and up to the randomization visit, any of the following types of infection

- Serious (requiring hospitalization, and/or IV or equivalent oral antibiotic treatment)
- Opportunistic (as defined in Winthrop at al. 2015; see Appendix 10.6).

  Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.
- Chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer)
- Recurring (including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis).

  Note: Participants with only recurrent, mild and uncomplicated orolabial and/or genital herpes may be discussed with the sponsor's designated medical monitor and may be considered for enrollment if other eligibility criteria are met.

[21] Have human immunodeficiency virus (HIV) infection

[22] Have a current or past infection with hepatitis B virus (HBV) (that is, positive for hepatitis B surface antigen [HBsAg] and/or hepatitis B core antibody) (see Section 8.2.7).

[23] Have a current infection with hepatitis C virus (that is, positive for HCV ribonucleic acid [RNA]).

[24] Have current or past history of active tuberculosis (TB) (see Section 8.2.6).

[25] Have or have had LTBI that has not been treated with a complete course of appropriate therapy as defined by the World Health Organization and/or the United States Centers for Disease Control and Prevention, unless such treatment is underway (see Section 8.2.6).

Vaccines

[26] Have received a Bacillus Calmette-Guerin (BCG) vaccination or treatment within 12 months before screening; or received any live vaccine (that is, live attenuated) within 3 months before screening, or intend to receive a live vaccine (or live attenuated) during the study. Note: Use of nonlive (inactivated) vaccinations is allowed for all participants.

Other medical conditions or history

[27] Have a diagnosis or history of malignant disease within 5 years before baseline (the randomization visit), with the following exceptions:

- basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years
- cervical carcinoma in situ, with no evidence of recurrence within the 5 years prior to baseline.

[28] Have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) **or**

have answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS,

and the ideation or behavior occurred within 4 weeks prior to screening and up to the randomization visit.

[29] Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.

[30] Have significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the IP; or of interfering with the interpretation of data.

[31] Are immunocompromised.

[32] Have clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin [Ig] A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).

[33] Have significant allergies to humanized monoclonal antibodies or any components of the LY3041658 product formulation.

Diagnostic assessments

[34] Have screening electrocardiogram (ECG) abnormalities that, in the opinion of the investigator, are clinically significant and indicate an unacceptable risk for the participant's safety in the study.

[35] Have any of the following specific abnormalities on screening laboratory tests:

a. Creatinine ≥2 times ULN

b. AST or ALT ≥2 times ULN

c. Alkaline phosphatase (ALP) ≥2 times ULN

d. Total bilirubin level (TBL) ≥1.5 times ULN

e. Hemoglobin <9.0 g/dL (<90.0 g/L)

f. Total white blood cell (WBC) count <2500 cells/μL (<2.50x10^3/μL or <2.50 GI/L)

g. Neutropenia (absolute neutrophil count <1200 cells/μL) (<1.20x10^3/μL or <1.20 GI/L)

h. Lymphopenia (absolute lymphocyte count <750 cells/μL) (<0.75x10^3/μL or <0.75 GI/L)

i. Thrombocytopenia (platelet count <100,000 cells/μL) (<100x10^3/μL or <100 GI/L)

Note: For each aforementioned test, 1 repeat testing is allowed during screening, and values resulting from repeat testing may be accepted for a participant's enrollment eligibility if the other eligibility criteria are met (see Section 5.4.1).

Prior or concurrent clinical study experience

[36] Have participated, within the last 30 days before baseline (the randomization visit), in a clinical trial involving any investigational product (IP) . If the previous IP has a half-life of greater than 7 days, at least 3 months or 5 half-lives (whichever is longer) should have passed before enrollment in this study.

[37] Have previously completed or withdrawn from this study or from any other study investigating LY3041658, and have previously received the IP.

[38] Are currently enrolled in any other clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study.

Other exclusions

[39] Are pregnant or breastfeeding, or intend to become pregnant or breastfeed during the study.

[40] Have donated more than a single unit of blood within 4 weeks prior to the screening visit or intend to donate blood during the course of the study.

[41] Have no contraindication to, and in the investigator's opinion are candidate for use of, at least one of the following: chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in water.

[42] Are investigative site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[43] Are employees of Eli Lilly and Company (Lilly) or are employees of a third-party organization involved in the study which requires exclusion of their employees.

[44] Are, in the opinion of the investigator or sponsor, unsuitable for inclusion in the study.

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event.

5.4.1. Allowed Retesting of Screening Investigations

Repeating laboratory tests during the screening period does not constitute rescreening.

See Section 8.2.6 for retesting related to TB.

5.4.2. Rescreening of Individuals Who Failed Screening

Informed consent for rescreenings

Individuals who are to be rescreened must first sign a new ICF (Appendix 10.1, Section 10.1.3). Such individuals will be assigned a new participant number.

Rescreening after failure to meet study eligibility criteria

An individual who does not meet the criteria for participation in this study may be rescreened **one time** if the reason for the screen failure has resolved and if the sponsor has approved the rescreening. The interval between the failure to meet study entry criteria and the start of rescreening should be at least 4 weeks.

Allowed rescreening for administrative reasons

An individual may be rescreened **one time** for an administrative reason such as falling out of the screening window because of scheduling conflicts. The sponsor does not need to approve rescreening for an administrative reason. The rescreening can start immediately after the administrative reason has resolved.

Procedures not required to be repeated during rescreening

Individuals in rescreening who have already completed the protocol-required ECG, screening chest x-ray (CXR), or TB tests are not required to repeat these procedures if these procedures

were performed within 90 days before the date of signing the ICF for rescreening. However, these procedures can be repeated at the discretion of the investigator.

All other screening procedures must be repeated during rescreening to ensure that all the study eligibility criteria are met.

6. Study Intervention

Study intervention is defined as any investigational intervention, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

6.1. Study Interventions Administered

Study interventions

This study involves one dose level of LY3041658 and placebo, as shown below.

Treatment Name	LY3041658	Placebo
Dosage Formulation	3-mL vial delivers 300 mg LY3041658	0.9% sodium chloride
Dosage Levels	600 mg	not applicable
Routes of Administration	IV	IV
Dosing Instructions	One dose every 2 weeks	One dose every 2 weeks

Abbreviation: IV = intravenous.

LY3041658 drug product will be provided as a solution formulation in a glass vial. The drug product vials will be supplied in cartons, with the appropriate quantity specific to the planned dispensing schedule of the IPs.

When the dosing solutions are prepared according to the provided instructions (Section 6.2) it will not be possible to distinguish LY3041658 from placebo.

Monitoring after dose administration

All participants should be monitored for 30 minutes or longer after completion of each IV infusion, according to investigator practice or local standard of care.

Sites must have resuscitation equipment, emergency drugs, and appropriately trained staff available during the infusion and monitoring period, or until completion of all required post-dosing activities (whichever is longer).

Packaging and labeling

Study interventions (LY3041658 and placebo) will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice (cGMP). Clinical trial materials will be labeled according to the country's regulatory requirements. All IPs will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

6.2. Preparation/Handling/Storage/Accountability

The Pharmacy Manual provides instructions for the preparation, handling, and storage of LY3041658 drug product and placebo, and describes site responsibility and accountability for the administered products.

Investigators should consult the information provided in the Pharmacy Manual or the label for specific administration information, including warnings, precautions, contraindications, adverse reactions, and dose modifications.

Preparation

The IPs must be prepared by an unblinded pharmacist (or other unblinded qualified individual) who is not involved in any other study-related procedures.

Handling and storage

Follow the storage and handling instructions on the IP packaging.

Site responsibilities and accountability

The following are responsibilities of the investigator or his or her designee:

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

The investigator or designee is also responsible for

- explaining the correct use of the study interventions
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensing and collection, and
- returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

Blinding will be maintained throughout the conduct of the study as described in the separate Unblinding Plan.

Method of treatment assignment

Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

Unblinded pharmacist

Investigators and all individuals involved in administering the blinded treatment or performing assessments will remain blinded to each participant's assigned study intervention throughout the study's blinded treatment period. To maintain this blind, an otherwise uninvolved party (unblinded pharmacist or other unblinded qualified individual) will be responsible for the reconstitution and dispensation of all study intervention. Blinded site personnel will administer the intervention to the participant.

Emergency unblinding

Emergency unblinding for adverse events may be performed through the IWRS. This option may be used ONLY if the participant's well-being requires knowledge of the participant's treatment assignment. All actions resulting in an unblinding event are recorded and reported by the IWRS.

If a participant's study treatment assignment is unblinded to the investigator, to site personnel performing assessments, or to the participant, the participant must be discontinued from the study, unless the investigator obtains specific approval from the sponsor's medical monitor for the participant to continue in the study (Section 7.1.1).

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify the sponsor as soon as possible.

In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor clinical research physician (CRP) for the participant to continue in the study.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee at the study site, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). Deviations from the prescribed dosage regimen should be recorded in the eCRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with

- Reason for use
- Dates of administration including start and end dates, and
- Dosage information, including dose for concomitant therapies of special interest.

Participants will be instructed to consult the investigator or other appropriate study site personnel before taking any new medications or supplements during the study.

The sponsor's medical monitor should be contacted if there are any questions.

6.5.1. Washout Period Before Enrollment

For the following medications, participants must complete a washout period before enrolling in the study, as stated in Section 5.1 and Section 5.2:

- topical antibiotics for HS
- oral opioids for HS-related pain
- systemic (including oral) antibiotic or anti-infective treatments except those taken for HS (see Section 6.5.2) or latent TB

  Note: A participant taking oral antibiotics for HS at the screening visit may continue them if the participant intends to continue them for the duration of the study (Section 5.1).
- systemic non-biologic immunosuppressant, and
- biologic taken for any indication other than HS.

6.5.2. Permitted Concomitant Therapy

The following will be required as concomitant therapy during the study:

- one of the following over-the-counter topical antiseptics to be used on body areas affected with HS lesions:
  - chlorhexidine gluconate
  - triclosan
  - benzoyl peroxide, or
  - dilute bleach in water.

Other medications are permitted during the study, including, but not limited to, these:

- wound care dressings: alginates, hydrocolloids, and hydrogels
- oral antibiotics: Participants on a stable dose of an oral antibiotic for HS before screening must remain on the same stable dose throughout the study, unless a change is required for the participant's safety. The permitted oral antibiotics will be recorded on the eCRF as concomitant medications.
- CBD products derived exclusively from hemp: Participants who use these products must be on a stable dose before the randomization visit and remain on the stable dose throughout the study.

6.5.3. Rescue Therapy

Participants who need rescue pain management during the study will be allowed to use the following, alone or in combination:

- tramadol, NSAIDs, or acetaminophen

- intra-lesional triamcinolone, or equivalent corticosteroid, injection (10 mg/mL triamcinolone, maximum 1 mL/lesion; a given lesion should receive injections no more than every 2 weeks), and
- incision and drainage.

Unscheduled visits are allowed for acutely painful lesions requiring intervention (either intra-lesional triamcinolone or incision and drainage).

An intervention can occur on maximally 2 different lesions at the same visit or on the same lesion at 2 different study visits. The same lesion cannot be treated 2 times at the same visit.

6.5.4. Prohibited Concomitant Therapy

The following will be prohibited as concomitant therapy during the study:

- topical antibiotics for HS
- any biologic agent, whether marketed or investigational
- any non-biologic systemic immunosuppressant
- oral opioids for HS-related pain, and
- cannabis (marijuana).

6.5.5. Therapy After Permanent Discontinuation of Study Drug

The restrictions on concomitant therapy described above are applicable to participants throughout the study, including any periods of time off study drug such as the post-treatment follow-up period.

6.6. Dose Modification

Modification of the dose of the study intervention is not permitted in this study.

6.7. Intervention after the End of the Study

LY3041658 will not be available to participants following completion of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

In rare instances, it may be necessary for a participant to permanently discontinue study drug.

These sections describe reasons for a participant's

- permanent or temporary discontinuation of study drug (Section 7.1), or
- discontinuation (withdrawal) from the study (Section 7.2).

Discontinuation of specific sites or of the trial as a whole are handled as part of regulatory, ethical, and trial oversight considerations in Appendix 10.1, Section 10.1.9.

7.1. Discontinuation of Study Intervention

Study drug may be permanently discontinued or temporarily withheld during the study.

Participants who permanently discontinue study drug early will undergo early termination procedures, which include

- an ETV

  AND,

- post-treatment follow-up visits, as shown in the SoA (Section 1.3).

7.1.1. Criteria for Permanent Discontinuation of Study Drug

Data collection and safety follow-up when study drug is permanently discontinued

If study drug is permanently discontinued, the participant will remain in the study to have an ETV, as well as post-treatment follow-up visits, as shown in the SoA (Section 1.3).

See the SoA for data to be collected at the time of discontinuation and follow-up and for any further evaluations that need to be completed. Safety follow-up is as outlined in the SoA (Section 1.3), Section 8.2 ("Safety Assessments), and Section 8.3 ("Adverse Events and Serious Adverse Events").

Criteria for permanent discontinuation of study drug

Possible reasons leading to permanent discontinuation of study drug include, but are not limited to, the following:

Participant decision

- The participant requests to discontinue the study drug.

Prohibited concomitant medication use

- The participant requires treatment with a prohibited medication (Section 6.5.4).

Pregnancy

- The participant becomes pregnant during the study (see Section 8.2.5.1).

Safety considerations

- The participant develops any of the following conditions during the study:
  - malignancy (except for successfully treated basal or squamous cell skin carcinoma)
  - HIV/acquired immune deficiency syndrome (AIDS) infection
  - active TB infection (Section 8.2.6)
  - HCV RNA positive (Section 8.2.8)
- The participant answered yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, **or** answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS (Section 8.2.10).

  Note: A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.
- The investigator, after consultation with the sponsor's designated medical monitor, determines that a systemic hypersensitivity reaction has occurred and is related to study drug administration.
- The participant experiences any 1 of the following events on 2 consecutive samples taken at least 48 hours, but no more than 1 week, apart.
  - Total WBC <1000 cells/μL
  - Absolute neutrophil count (ANC) <500 cells/μL
  - Absolute lymphocyte count (ALC) <200 cells/μL
- The participant has an adverse event or serious adverse event or a clinically significant change in a laboratory value that, in the opinion of the investigator or sponsor, would preclude the participant from continuing to receive study drug.

Hepatic event or liver test abnormality

- Participants who are discontinued from study drug because of a hepatic event or liver test abnormality should have additional hepatic safety data collected via the hepatic eCRF packet. Discontinuation of study drug because of abnormal liver tests should be considered by the investigator when a participant meets one of the following conditions after consultation with the medical monitor (see Section 8.2.9).
  - ALT or AST >8 times ULN
  - ALT or AST >5 times ULN sustained for more than 2 weeks
  - ALT or AST >3 times ULN and TBL >2 times ULN or international normalized ratio (INR) >1.5
  - ALT or AST >3 times ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - ALP >3 times ULN
  - ALP >2.5 times ULN and TBL >2 times ULN, or

– ALP >2.5 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Other reasons

- Unblinding: If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study drug and continue to post-treatment follow-up. In cases where there are ethical reasons to have the participant continue on study drug, the investigator must obtain specific approval from the sponsor or designee for the participant to continue.

7.1.2. Criteria for Temporary Interruption (Withholding) of Study Drug

7.1.2.1. Infection-Related Criteria for Temporary Withholding of Study Drug

If a participant develops an infection, study intervention is to be withheld until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment.

7.1.2.2. Other Criteria for Temporary Withholding of Study Drug

Dosing may be interrupted and resumed in participants who experience the following reductions but do not meet the criteria for permanent discontinuation:

- interrupt if total WBC count is <2000 cells/μL (leukopenia) and resume when total WBC count is ≥2000 cells/μL
- interrupt if ANC is <1000 cells/μL (neutropenia) and resume when ANC is ≥1000 cells/μL
- interrupt if ALC is <500 cells/μL (lymphopenia) and resume when ALC is ≥500 cells/μL.

7.2. Participant Discontinuation/Withdrawal from the Study

Participant discontinuation (withdrawal from the study) is expected to be uncommon.

A participant may withdraw from the study in the following circumstances:

- at any time at his or her own request, or at the request of his or her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant enrolls in any other clinical study involving an investigational medicinal product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

Data collection and follow-up for participants who discontinue the study

At the time of discontinuing from the study, if possible, an ETV should be conducted, if possible, as shown in the SoA. See the SoA for data to be collected at the time of study discontinuation

and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study.

Withdrawal of consent for disclosure

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor's clinical research physician agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor's clinical research physician to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational medicinal product. Safety follow-up is as outlined in the SoA (Section 1.3), Section 8.2 ("Safety Assessments), and Section 8.3 ("Adverse Events and Serious Adverse Events").

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All assessments and sample collections should be finished before a dose is administered at the dosing visits.

8.1. Efficacy Assessments

Order of efficacy assessments

Efficacy assessments should be timed so that participants' self-assessments are completed before clinical assessments or sample collections are performed.

Appropriateness of efficacy assessments

The primary measure of disease activity, HiSCR, has been recognized as a valid and meaningful endpoint and has been used in previous HS trials (Section 4.2). The secondary and exploratory measures of disease activity and quality of life are also generally recognized as reliable, accurate, and relevant.

The patient-reported outcomes (PRO) questionnaires will be administered electronically and only in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

8.1.1. Lesion Assessments: Count, Measurement, and Severity

At the visits designated in the SoA (Section 1.3), the investigator will examine the participant's skin. Using an electronic device, the investigator will record which anatomical regions have lesions, the type and number of lesions, and the Hurley stage for each affected region.

The anatomical regions are to be examined for lesions are these:

- left axilla
- right axilla
- left inframammary area
- right inframammary area
- intermammary area
- left buttock
- right buttock
- left inguino-crural fold
- right inguino-crural fold
- perianal area
- perineal area, and
- other.

The types of lesions to be counted and recorded are these:

- abscesses (A)
- draining fistulas (DF)
- nondraining fistulas (F),

- inflammatory nodules (N)
- non-inflammatory nodules (xN)

The severity stages (Hurley stages [1989]) to be assigned and recorded are these:

Stage I: Abscess formation, single or multiple, without sinus tracts and cicatrization

Stage II: Recurrent abscesses with tract formation and cicatrization, single or multiple, widely separated lesions

Stage III: Diffuse or near diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.

For each anatomical region, the investigator will measure and record the longest distance between 2 relevant lesions. If there is only 1 lesion, the investigator will measure and record the diameter of that lesion. The investigator will also determine and record (as yes or no) whether the lesions are clearly separated by normal skin.

To reduce inter-rater variability, the investigative site personnel should attempt to ensure that a participant's lesions are assessed by the same investigator throughout the study.

The lesion assessments by the investigator are used to calculate HiSCR, modified Sartorius Score (mSS), and International Hidradenitis Suppurativa Severity Score System (IHS4).

8.1.1.1. Hidradenitis Suppurativa Clinical Response (HiSCR)

The HiSCR (Kimball et al. 2014; Kimball et al. 2016b) is defined as at least a 50% reduction in the total abscess and inflammatory nodule count (sum of abscesses and inflammatory nodules [AN count]) with no increase in abscess count (A count) and no increase in draining fistulae count (DF count) relative to baseline.

8.1.1.2. Modified Sartorius Score (mSS)

The mSS (Sartorius et al. 2009) is a measure for disease severity calculated by the investigator's assignment of a score to each anatomical region based on the

- presence of lesions (3 points if at least 1 lesion is present; 0 if no lesion is present)
- number and type of lesions in each region (each fistula = 6 points; each nodule = 1 point)
- longest distance between relevant lesions within each region or else the diameter of the lesion if the region has only 1 lesion (≥10 cm = 9 points; <10 cm and ≥5 cm = 3 points; <5 cm = 1 point; 0 points if no lesion), and
- presence of normal skin clearly separating all lesions (no [that is, Hurley stage III] = 9 points; yes = 0 points).

A participant's total mSS is the sum of his or her regional Sartorius scores. Higher mSS scores, for which there is no predefined upper limit, indicate increasingly severe disease.

8.1.1.3. International Hidradenitis Suppurativa Severity Score System (IHS4)

The IHS4 score (Zouboulis et al. 2017) is a measure of disease severity calculated by summing the number of

- nodules multiplied by 1
- abscesses multiplied by 2, and
- draining tunnels multiplied by 4.

A total score of 3 or less signifies mild disease, 4 to 10 signifies moderate disease, and 11 or greater signifies severe disease.

8.1.2. Skin Pain – HS Numeric Rating Scale (NRS)

The Skin Pain – HS Numeric Rating Scale (NRS) is a patient-administered, single-question, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "pain as bad as I can imagine." The recall period is 7 days.

8.1.3. Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a participant-rated, 10-item questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the "last week." Response categories include "a little," "a lot," and "very much," with corresponding scores of 1, 2, and 3, respectively, and "not at all" or unanswered ("not relevant") responses scored as 0. Scores range from 0 to 30, with higher scores indicating greater impairment of quality of life. A DLQI total score of 0 to 1 is considered as having no effect on a participant's health-related quality of life (Hongbo et al. 2005), and a 4-point change from baseline is considered the minimal clinically important difference threshold in patients with inflammatory skin disease (Basra et al. 2015).

8.1.4. Drainage Numeric Rating Scale (NRS)

The Drainage Numeric Rating Scale (NRS) is a patient-rated, single-question, 11-point horizontal scale anchored at 0 and 10, with 0 representing "No drainage" and 10 representing "Drainage as bad as I can imagine." The recall period is 7 days.

8.1.5. Smell Numeric Rating Scale (NRS)

The Smell Numeric Rating Scale (NRS) is a patient-rated, single-question, 11-point horizontal scale anchored at 0 and 10, with 0 representing "No smell" and 10 representing "Smell as bad as I can imagine." The recall period is 7 days.

8.1.6. Patient's Global Impression of Severity – 7 Days (Hidradenitis Suppurativa)

The Patient's Global Impression of Severity – 7 Days for HS is a single-item question asking the participants how they would rate their overall HS severity over the past 7 days. The 5 categories of response are "no symptoms," "very mild," "mild," "moderate," and "severe."

8.1.7. Patient Global Impression of Change - 7 Days (Hidradenitis Suppurativa)

The Patient Global Impression of Change – 7 Days for HS is a single-item question asking the participants how they would rate the change in their HS symptoms since they started taking the study medication. The 5 categories of response are "much better," "a little better," "no change," "a little worse," and "much worse."

8.1.8. Inflammatory Back Pain Assessment (ASAS Expert Criteria) and Spinal Pain Numeric Rating Scale (NRS)

The presence of inflammatory back pain (IBP) will be assessed at baseline using Assessment of SpondyloArthritis International Society (ASAS) expert criteria adapted from Sieper et al. 2009. A participant is considered to have IBP when 4 of the 5 following parameters are present: 1) onset before the age of 40 years, 2) insidious (gradual or unperceived) onset, 3) improvement with exercise, 4) no improvement with rest, 5) pain at night with improvement upon getting up.

Participants meeting the IBP criteria at baseline will be asked questions about spinal pain during the study. They will be asked to respond to the following 2 questions (on average during the last week):

1. "How much pain of your spine do you have?"
2. "How much pain of your spine do you have at night?"

The answers are recorded on an NRS and are each rated between "0" (no pain) and "10" (most severe pain).

8.2. Safety Assessments

Order of safety assessments

If multiple safety assessments are scheduled to occur during the same visit, the preferred order of completion is

1) ECG (if applicable) and vital signs first
2) other safety assessments, including physical examinations and nonleading (spontaneous) adverse event collection, followed by C-SSRS (Section 8.3.1.1), and finally
3) sample collection for clinical laboratory, PK, pharmacodynamic (PD), pharmacogenetic, biomarker, and immunogenicity testing.

Data collection and reporting

The adverse event data collection and reporting requirements are described in Section 8.3 and Appendix 10.3. Additional requirements regarding adverse events of special interest (AESIs) are described in Section 8.3.

Any clinically significant findings that result in a diagnosis and that occur after the participant receives the first dose of study drug should be reported to Lilly or its designee as an adverse event via eCRF.

Safety monitoring

The principle investigator will monitor safety and laboratory data throughout the study and should discuss immediate safety concerns with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue the study intervention.

The sponsor will monitor the safety data, including adverse events and serious adverse events (SAEs), discontinuations, medical history, concomitant medications, vital signs, and clinical laboratory results by means of periodic blinded reviews and other appropriate methods. These

methods include reviews by a functionally independent safety physician and/or clinical research scientist who regularly reviews SAE reports in real time and across studies, and who reviews applicable clinical safety and epidemiological publications from the literature. If this safety monitoring uncovers an issue that needs to be addressed by unblinding at the individual or group level, additional analyses of the safety data can be performed by the sponsor's independent internal safety review committee (Appendix 10.1, Section 10.1.5).

Appropriateness of safety assessments

The safety assessments used in this study are routine elements of clinical health assessment and Phase 2 drug development.

8.2.1. Vital Signs

Vitals signs (body temperature, blood pressure, and pulse rate) will be measured at the visits specified in the SoA (Section 1.3) and as clinically indicated. Additional vital signs may be measured during the study visits if warranted, as determined by the investigator.

Blood pressure and pulse rate should be measured after the participant has been sitting for at least 5 minutes. Orthostatic vital signs should be assessed, if possible, during any adverse event of dizziness or posture-induced symptoms. If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 3 minutes. If the participant feels unable to stand, only supine vital signs will be recorded.

8.2.2. Physical Examinations

A complete physical examination will be performed at the screening visit. This examination excludes pelvic, rectal, and breast examinations unless clinically indicated.

A symptom-directed physical examination will be performed at other visits, as specified in the SoA (Section 1.3) and as clinically indicated.

At the screening visit and at approximately every third month thereafter, the physical examination, whether it is complete or symptom-directed, should include an assessment of TB risk factors and symptoms or signs of TB, including an assessment of peripheral lymph nodes (Section 8.2.6).

Height (without shoes) and weight will also be measured and recorded as specified in the SoA.

8.2.3. Electrocardiograms

For each participant, 12-lead ECGs will be collected as specified in the SoA (Section 1.3). Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of additional ECGs at a particular time point is allowed to ensure high quality records.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the study site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets the study entry criteria and for immediate participant management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT/QTc interval from baseline), the investigator or qualified designee, in conjunction with the sponsor's medical monitor, will determine if the participant can continue in the study and if any change in participant management is needed.

The investigator or qualified designee must document his or her review of the ECG printed at collection. Any new clinically relevant finding will be reported as an adverse event.

8.2.4. Chest Radiography (CXR)

A posterior–anterior (PA) chest x-ray (CXR), interpreted and reported by a radiologist or pulmonologist, will be obtained as specified in the SoA (Section 1.3).

A lateral CXR can also be obtained if, in the opinion of the investigator, a lateral view is indicated.

> Note: Participants do not need to have a CXR at screening if, based on the judgment of the investigator, both of the following 2 conditions are met:
>
> - the CXR was performed within 6 months before initial screening, and
> - documentation of the CXR, read by a qualified radiologist or pulmonologist, is sufficient for TB evaluation according to local standard of care.

For each participant, the CXR films or images or a radiology report must be available to the investigator for review before the participant is randomized. Certain findings from CXR may be consistent with a condition that excludes a participant from the study; see Section 5.2.

> Note: Results of a chest computerized tomography (CT) scan or other imaging study similar to a CXR may be substituted in place of the CXR as described above, in consultation with the sponsor's medical monitor.

8.2.5. Laboratory Tests

Appendix 10.2 lists the clinical laboratory tests to be performed, and the SoA (Section 1.3) specifies the study visits at which samples are collected for clinical laboratory tests.

Samples for laboratory testing will be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions, as described in Section 8.3.6.2 and Appendix 10.2.

Additional tests may be performed at any time during the study as deemed necessary by the investigator or as required by local regulations.

All protocol-required laboratory assessments, as defined in Appendix 10.2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or adverse event or dose modification), then the results must be recorded in the CRF.

Reviewing and recording test results

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF.

The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

Repeat testing after clinically significant abnormal findings

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 12 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Blinding of laboratory test results

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel (Appendix 10.2).

Sample retention

Unless otherwise specified in the subsections of Section 8 or in Appendix 10.1, Section 10.1.12 ("Long-Term Sample Retention"), all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.2.5.1. Pregnancy Testing

Pregnancy testing is to be performed on women of childbearing potential (WOCBP) and women with a history of tubal ligation. Participants who are pregnant will be discontinued from the study (Section 7.1.1).

Visits and times

Serum pregnancy test will be done at screening only, and results will be confirmed by the central laboratory.

Urine pregnancy testing will be performed locally, as specified in the SoA (Section 1.3). If the specified visit includes study drug administration, the urine pregnancy test must be "negative" within 24 hours before the study drug is administered.

Urine pregnancy testing may be performed at additional time points during the study treatment period and/or follow-up period, at the discretion of the investigator or if this is required by local regulations.

If a urine pregnancy test is not available, a local serum pregnancy test is an acceptable alternative.

Optional follicle-stimulating hormone (FSH) testing

The participant's FSH level can be obtained during screening at the discretion of the investigator to assist in determining whether a woman meets the definition of "postmenopausal." The FSH level can also be optionally obtained during the study to determine the participant's postmenopausal status (see Section 1.3 and Section 10.4.1).

8.2.6. Tuberculosis Testing and Monitoring

Tuberculosis testing

During screening, all participants are to be assessed for risk factors, symptoms, and signs of TB with all of the following:

- Thorough history to determine the lifetime risk factors for TB infection, for TB progression, and for symptoms and/or signs of active TB, and
- Signs of previous or active TB by means of
  - Thorough physical examination for signs of active TB, including measurement of body temperature (Section 8.2.1) and assessment of peripheral lymph nodes (Section 8.2.2), and
  - PA CXR interpreted and reported by radiologist or pulmonologist (Section 8.2.4).

All participants with no history of LTBI or active TB, and no history of positive Mantoux tuberculin skin test (TST) using purified protein derivative (PPD) or positive *Mycobacterium tuberculosis* interferon gamma release assay (IGRA) must have one of the following:

- Purified Protein Derivative (PPD) TST
  - The TST is performed by injecting 0.1 mL of tuberculin PPD into the inner surface of the forearm. The injection should be made with a tuberculin syringe. The TST is an intradermal injection. When placed correctly, the injection should produce a pale elevation of the skin (a wheal) 6 to 10 mm in diameter. Measure induration at site of intradermal injection 48 to 72 hours after intradermal injection. The test must be read during this window of time. The reaction should be measured in millimeters of induration (palpable, raised, hardened area or swelling). The reader should not measure erythema (redness). The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis).
  - An induration of 5 or more millimeters is considered positive in
    - HIV-infected persons
    - A recent contact of a person with TB disease
    - Persons with fibrotic changes on chest radiograph consistent with prior TB
    - Persons with organ transplants
    - Persons who are immunosuppressed for other reasons (for example, taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking tumor necrosis factor-α antagonists).
  - An induration of 10 or more millimeters is considered positive in all other potential clinical trial participants.
  - Two-step testing (repeat TST from 1 to 3 weeks after the first TST) is recommended for certain participant groups, including:
    - Persons receiving immunosuppressant treatment

- ¤ Persons with a history of temporally remote increased risk of TB infection
- ¤ Persons for whom the first test is negative, as per local public health and/or professional medical society recommendations.

- Interferon Gamma Release Assay (IGRA) for *M tuberculosis*. Ensure that specimen handling, transport, timing, and laboratory procedures meet all requirements per package insert. If the investigator suspects a false-positive IGRA result in a participant with no increased risk of TB infection during lifetime, and no evidence of prior or current TB on physical examination and/or on CXR interpreted by radiologist and/or pulmonologist (investigator assessment by history and physical examination, and CXR report documented in eCRF), the investigator may discuss retesting with the sponsor's designated medical monitor.

Retesting

One retest is allowed for participants with an "indeterminate" QuantiFERON-TB Gold assay or "borderline" T-SPOT.TB assay. Participants with 2 indeterminate QuantiFERON-TB Gold assays or 2 borderline T-SPOT.TB assays will be excluded.

Diagnosed LTBI

Participants diagnosed with LTBI are excluded (Section 5.2) unless they are candidates for LTBI treatment, are treated for LTBI, and the following criteria are met:

- After receiving at least 4 weeks of appropriate LTBI therapy (as per World Health Organization and/or the United States Centers for Disease Control guidelines), there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) or other treatment intolerance. The participant may be rescreened, and is not excluded due to LTBI.
- The participant must continue and complete appropriate LTBI therapy in order to remain eligible to continue to receive study intervention.

Monitoring during the study

For all participants, monitoring for TB is to be continuous throughout the study. At a minimum, each participant is to have the following documented at least every 3 months:

- Thorough history to determine any risk factors for TB infection and for TB progression, symptoms or signs of active TB, and
- Physical examination that includes assessment for signs of active TB, including measurement of body temperature and assessment of peripheral lymph nodes.

8.2.7. Hepatitis B Testing and Monitoring

Initial testing for HBV infection includes hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (anti-HBc):

- If HBsAg is positive, the participant is excluded.
- If HBsAg is negative and anti-HBc is negative, the participant is not excluded.
- If HBsAg is negative and anti-HBc is positive, the participant is excluded.

8.2.8. Hepatitis C Testing and Monitoring

Initial testing for HCV infection includes testing for antibodies to HCV.

- If anti-HCV is positive, a test for circulating HCV RNA is required.
- If HCV RNA test is negative, the participant is not excluded.
- If HCV RNA test is positive, the subject is excluded (see Section 5.2).

Participants who have had HCV infection and been successfully treated, defined as a sustained virologic response (HCV RNA by PCR negative for at least 24 weeks following treatment completion) are not excluded on the basis of HCV as long as HCV RNA test is negative at screening.

If HCV RNA is detected during the study, the study drug will be discontinued (Section 7.1.1), and the participant should receive appropriate follow-up medical care.

8.2.9. Hepatic Safety Monitoring

Close hepatic monitoring

If a study participant experiences

- ALT or AST ≥3 times ULN,
- ALP ≥2 times ULN, or
- TBL ≥2 times ULN (except for patients with Gilbert's syndrome),

the laboratory tests listed in Appendix 10.5, including ALT, AST, ALP, TBL, direct bilirubin, GGT, and creatine kinase (CK), should be repeated within 48 to 72 hours, to confirm the abnormality and to determine whether it is increasing or decreasing.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for the possible causes of the abnormal liver tests should be initiated by the investigator in consultation with the sponsor's designated medical monitor. At a minimum, this evaluation should include a physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking, and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

If a study participant experiences:

- ALT or AST ≥3 times ULN with hepatic signs/symptoms (severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.),
- ALT or AST ≥5 times ULN,
- ALP ≥3 times ULN,

- TBL ≥2 times ULN (except for patients with Gilbert's syndrome),

the evaluation should include a physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time (PT-INR); viral hepatitis A, B, C, and E; tests for autoimmune hepatitis, and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the sponsor's designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy.

8.2.9.1. Hepatic Safety eCRF

The following list describes when additional hepatic safety data collection in the hepatic safety eCRF should be done:

- ALT to ≥5 times ULN on 2 or more consecutive blood tests
- ALP to ≥2 times ULN on 2 or more consecutive blood tests
- TBL to ≥2 times ULN (except for cases of known Gilbert's syndrome)

  Note: the interval between the 2 consecutive blood tests should be at least 2 days.

Additional criteria include

- a hepatic event considered to be an SAE, and
- discontinuation of study intervention due to a hepatic event (Section 7.1.1).

8.2.10. Suicidal Ideation and Behavior Risk Monitoring

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of intervention. Participants who have signs of suicidal ideation or behavior should be considered for discontinuation of study drug, following a risk assessment (see Section 7.1.1). See Section 8.3.1.1 for timing of adverse event collection relative to collection of the C-SSRS.

8.2.10.1. Columbia Suicide-Severity Rating Scale (C-SSRS)

The Columbia Suicide-Severity Rating Scale (C-SSRS) is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health (NIMH) trial group (TASA) for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events.

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or SAE and remain responsible for following up adverse events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study (see Section 7).

Pregnancy after maternal or paternal exposure to investigational product does not meet the definition of an adverse event. However, to fulfill regulatory requirements, any pregnancy should be reported using the SAE process described in Appendix 10.3, Section 10.3.4, to collect data on the outcome for both mother and fetus. See also Section 8.3.5.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All adverse events will be collected from the time of the participant’s signing of the ICF until the participant’s last post-treatment follow-up visit.

Likewise, all SAEs will be collected from the signing of the ICF until the last post-treatment follow-up visit.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event CRF.

Although all adverse events after signing the ICF are recorded by the site in the CRF/electronic data entry tool, SAE reporting to the sponsor begins after the participant has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF but prior to receiving study drug, the SAE needs to be reported ONLY if the SAE is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or the sponsor’s designee immediately, and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse events or SAEs after the conclusion of study participation, that is, once the participants have discontinued and/or completed the study (the Participant Study Disposition eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire

Nonleading (spontaneous) adverse event collection should occur before the collection of the C-SSRS.

If a suicide-related event is discovered during the C-SSRS collection but was not captured during the nonleading adverse event collection, sites should not change the adverse event form. However, if an adverse event is serious or leads to discontinuation, the adverse event should be included on the adverse event form. Also, the process for reporting SAEs should be followed.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

Care will be taken not to introduce bias when detecting adverse events and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs, as defined in Section 8.3.6, "Adverse Events of Special Interest"), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3, Section 10.3.3.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

For female participants and female partners of male participants, details will be collected for pregnancies occurring from after the start of study intervention and until 12 weeks after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 10.4, Section 10.4.3.

Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interest

Adverse events of special interest for this study include infusion reactions, systemic hypersensitivity reactions, and infections. If such adverse events are reported, sites will be prompted to collect additional data as described in the following subsections.

8.3.6.1. Infusion Site Reactions

Symptoms of a local infusion site reaction may include erythema, induration, pain, pruritus, and edema. If an infusion site event is reported, the adverse event will be recorded, and additional data will be provided to the sponsor in the eCRF.

8.3.6.2. Systemic Hypersensitivity Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the eCRF.

Sites should have appropriately trained medical staff and appropriate medical equipment available when the study participants are receiving study drug. Participants who experience a systemic hypersensitivity reaction should be treated per the local standard of care.

Blood sample collection for systemic hypersensitivity reactions

In the case of generalized urticaria or anaphylaxis, additional blood samples should be collected as described in Appendix 10.2, Section 10.2.2. Laboratory results are provided to the sponsor via the central laboratory.

8.3.6.3. Infections

Completion of the Infection eCRF page is required for each infection reported as an adverse event or SAE. The sponsor will identify infections considered to be opportunistic based on the article by Winthrop et al. (2015) (Appendix 10.6).

8.3.7. Complaint Handling

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a trial intervention. The sponsor collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the investigational product so that the situation can be assessed. Note: Any adverse events/SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.3 and Appendix 10.3.

Time period for detecting product complaints

Product complaints that result in an adverse event will be detected, documented, and reported to the sponsor during all periods of the study in which the drug/device is used. If the investigator learns of any product complaint at any time after a participant has been discharged from the

study, and such incident is considered reasonably related to a drug/device provided for the study, the investigator will promptly notify the sponsor.

Prompt reporting of product complaints to sponsor

Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint. The Product Complaint Form will be sent to the sponsor by a method designated by the sponsor.

Follow-up of product complaints

Follow-up applies to all participants, including those who discontinue study intervention. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint. New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

8.4. Treatment of Overdose

For this study, an overdose of LY3041658 is considered any dose higher than the dose assigned through randomization. In case of suspected overdose, hematology, chemistry, vital signs, and oxygen saturation should be monitored and supportive care provided as necessary.

In the event of an overdose, the investigator should:

1. Contact the sponsor's medical monitor immediately.
2. Closely monitor the participant for any adverse event or SAE and laboratory abnormalities until the study intervention can no longer be detected systemically, that is, approximately 12 weeks.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the sponsor's medical monitor based on clinical evaluation of the participant.

8.5. Pharmacokinetics

Visits and times

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine the plasma concentrations of LY3041658. The actual date and time (24-hour clock time) of dosing and sample collection must be recorded accurately on the appropriate forms.

Collection, handling, and analysis of samples

Instructions for the collection and handling of blood samples will be provided by the sponsor. Samples will be analyzed at a laboratory approved by the sponsor. Concentrations of LY3041658 will be assayed using a validated PK assay. Analyses of samples collected from participants who received placebo are not planned.

Additional and unused samples

A maximum of 3 additional samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Any excess samples collected for PK testing may be used for exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

In the case of systemic allergic/hypersensitivity reactions, additional blood samples will be obtained for PK analyses (Section 8.3.6.2).

Blinding

Drug concentration information that may unblind the study will not be reported to investigative sites or to personnel who are blinded to study data.

Sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Appendix 10.1, Section 10.1.12.

8.6. Pharmacodynamics

The exploratory pharmacodynamics (PD) endpoints include IL-8 and hs-CRP.

Visits and times

At the visits and times specified in the SoA (Section 1.3), blood samples will be collected for the exploratory analysis of PD endpoints.

Sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Appendix 10.1, Section 10.1.12.

8.7. Genetics

A whole blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3), where local regulations and ethical review boards (ERBs) allow.

Sample use

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Samples may be used for research related to LY3041658 and its mechanism of action, the drug target, genetic variants thought to play a role in HS, on the disease process and pathways associated with the disease or related diseases. The samples may also be used to develop tests or diagnostic tools or assays related to HS or to LY3041658. The samples may also be used to investigate variable exposure or response to LY3041658. The assessment of variable response may include evaluation of adverse events or differences in efficacy.

Molecular technologies are expected to improve during storage period and therefore cannot be specifically named. However, existing genetic research approaches include whole genome or exome sequencing, genome-wide association studies, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this protocol. The samples may be analyzed as part of single or multi-study assessment of genetic factors involved in the response to LY3041658 or to study interventions of

this class to improve understanding of the disease or related conditions, and additional analyses may be conducted if necessary to further understand the clinical data of this study.

Confidentiality

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigative site personnel. The sponsor will store the blood and/or deoxyribonucleic acid (DNA) samples in a secure storage space with adequate measures to protect confidentiality.

Sample retention

Samples will be retained at a facility selected by the sponsor or its designee. Samples will be retained as long as research on the study indication, study intervention, or the class of study intervention continues, but no longer than the maximum retention time specified in Appendix 10.1, Section 10.1.12.

8.8. Biomarkers

Serum and plasma for exploratory nonpharmacogenetic biomarker research will be collected at the visits and times specified in the SoA (Section 1.3), where local regulations allow.

Sample use

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of participant response (including safety), and/or clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules, including DNA for epigenetics, RNA, proteins, lipids, and other cellular elements.

Samples may be used for research on the drug target, disease process, variable response to LY3041658, pathways associated with HS, mechanism of action of LY3041658, and/or research methods or in validating diagnostic tools or assays related to HS or to LY3041658.

Confidentiality

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigative site personnel.

Sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Appendix 10.1, Section 10.1.12.

8.9. Immunogenicity Assessments

Visits and times

At the visits and times specified in the SoA (Section 1.3), predose blood samples will be collected to determine antibody production against LY3041658. The actual date and time (24-hour clock time) of each sample collection will be recorded.

If the immunogenicity sample at the last scheduled assessment or discontinuation visit is treatment-emergent (TE) anti-drug antibody (ADA) positive (as defined in Section 9.4.4.3),

additional samples may be taken until the potential signal returns to baseline (that is, no longer TE-ADA positive) or for up to 1 year after last dose.

To aid interpretation of these results, a predose blood sample for PK analysis will be collected at the same time points, as shown in the SoA.

Sample collection, handling, and use

Instructions for the collection and handling of blood samples will be provided by the sponsor.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3041658 at a laboratory approved by the sponsor. Antibodies may be further characterized for their ability to neutralize the activity of LY3041658.

Sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Appendix 10.1, Section 10.1.12.

8.10. Medical Resource Utilization and Health Economics

This section is not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

The study will compare LY3041658 with placebo in adults with HS. The primary study objective is to demonstrate superior efficacy of LY3041658 over placebo.

The primary comparison of interest is the proportion of participants achieving HiSCR response at Week 16.

Secondary comparisons include the mean change of AN count and Skin Pain – HS NRS from baseline to Week 16.

Efficacy comparisons will be made without regard to changes to any background therapies. No adjustments for multiplicity will be made across the efficacy assessments. Participants who discontinue the treatment or the study prior to Week 16 will be considered a nonresponder for all relevant analyses.

9.1.1. Estimands

The study will compare LY3041658 with placebo in participants with HS.

The primary comparison of interest is the difference in proportion of participants who achieve HiSCR response at Week 16. The primary objective is to demonstrate superiority of LY3041658 versus placebo.

The primary comparison will be assessed using a composite estimand where the intercurrent events of premature discontinuation and use of prohibited medication are part of the response definition.

9.2. Sample Size Determination

Approximately 100 patients will be screened to achieve approximately 63 participants randomized in a 2:1 ratio to one of two treatment groups:

- approximately 42 participants randomized to LY3041658, and
- approximately 21 participants randomized to placebo.

For all randomized patients, approximately 45 patients are expected to complete the 16 weeks' treatment period. This sample size provides at least 80% power to the primary endpoint of HiSCR response. This calculation is a 2-sided test for superiority of LY3041658 compared to placebo on HiSCR response rate with significance level of 0.05 CCI [redacted] CCI

9.3. Populations for Analyses

The following populations are defined for this study:

Population	Description
Entered	All participants who sign the informed consent form
Modified Intent-to-Treat (mITT)	All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention. Participants will be analyzed according to the intervention to which they were assigned.
Safety	All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received within each study period.
Pharmacokinetic (PK) Analysis	All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention and have PK data available.

9.4. Statistical Analyses

Statistical analysis of this study will be the responsibility of the sponsor or its designee.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) and clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to unblinding. It will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Efficacy analyses will be conducted on the Modified Intent-to-Treat (mITT) Population. This set includes all data from all randomized participants receiving at least 1 dose of the IP according to the treatment the participants were assigned.

Safety analyses will be conducted on the Safety Population. This set includes all data from all randomized participants receiving at least 1 dose of the IP according to the treatment the participants actually received.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All confidence intervals (CIs) will be given at a 2-sided 95% level. Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum, maximum, and sample size. Descriptive summaries of discrete data will report the number of participants and incidence as a frequency and as a percentage.

The baseline value for Treatment Period 1 is defined as the last nonmissing measurement on or before the date of first study drug administration (expected at Week 0). The baseline value for Treatment Period 2 is the last available value before Visit 10 (Week 16), the visit at which

participants who previously received placebo will receive their first dose of LY3041658. Other definitions of the baseline value may be used to conduct additional supporting analyses.

9.4.1.1. Participant Disposition

A description of participant disposition will be provided, including a summary of the number and percentage of participants entered into the study, enrolled in the study, and treated, as well as number and percentage of participants completing the study (participants who receive at least 1 dose of study drug and have at least 1 postbaseline assessment), or discontinuing (overall and by reason for discontinuation). A summary of important protocol deviations will be provided.

9.4.1.2. Participant Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target patient population. A summary of baseline participants and disease characteristics, historical diagnoses, pre-existing conditions, and prior therapies will be reported by cohort using descriptive statistics. Other participant baseline characteristics will be summarized by group as deemed appropriate.

9.4.1.3. Missing Data Imputation

Missing data on the primary endpoint, HiSCR response, will be imputed as nonresponse. For other endpoints, including continuous secondary endpoints, missing data may be imputed using the last observation prior to missingness or other appropriate imputation methods.

9.4.2. Primary Endpoint

The primary comparison of interest is the proportion of participants achieving HiSCR response at Week 16. The objective of the primary endpoint is to establish superiority of LY3041658 over placebo (see Section 9.4.1).

The primary endpoint will be analyzed using logistic regression on the mITT population. The treatment difference and 95% CIs will be reported.

9.4.3. Secondary Endpoints

Secondary comparisons of interest are the mean change from baseline to Week 16 for

- total number of abscesses and inflammatory nodules (AN count), and
- Skin Pain – HS NRS.

An analysis of covariance (ANCOVA) model will be used for analysis of these secondary endpoints.

9.4.4. Exploratory Endpoints

Exploratory analyses will be further described in the SAP that is finalized before database lock.

9.4.4.1. Patient-Reported Outcomes

Categorical variables will be analyzed using logistic regression analyses, whereas mixed-effects model of repeated measures (MMRM) will be the primary method of analysis for continuous endpoints. The analyses will be based on the mITT population, unless otherwise specified.

9.4.4.2. Pharmacokinetic Analyses

Plasma concentrations of LY3041658 will be listed by time point using descriptive statistics. The data may also be analyzed using a population approach via nonlinear mixed effects modeling (NONMEM) with the NONMEM software. The PK data from Study DSAD may be combined with data from another study in the clinical development program to improve PK parameter estimation.

9.4.4.3. Evaluation of Immunogenicity

Frequencies and percentages will be tabulated for the following:

- participants with pre-existing ADA, and
- participants who are TE-ADA positive (TE-ADA+) to LY3041658.

Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA). For the TE-ADA+ participants, the distribution of maximum titers will be described. The frequency of neutralizing antibodies, if assessed, may also be tabulated for the TE-ADA+ participants.

The relationship between the presence of ADA and the LY3041658 concentrations and PD response to LY3041658, including safety and efficacy, may also be assessed. Additional details may be provided in the SAP.

9.4.4.4. Other Exploratory Endpoints

Exploratory efficacy endpoint data, PD data, and biomarker data will be analyzed as described in the SAP. Relationships between LY3041658 exposure and select biomarkers and clinical efficacy endpoints may be explored.

9.4.5. Safety Analyses

Safety analyses will include adverse events, SAEs, AESIs, C-SSRS, vital signs, ECGs, and laboratory analytes, using the Safety Population data descriptively summarized by treatment group. Categorical safety measures will be summarized with incidence rates. Continuous safety measures will be summarized as mean change by visit. Exposure to study intervention will be calculated for each participant and summarized by treatment group.

Adverse events will be coded according to the *Medical Dictionary for Regulatory Activities* (MedDRA) and summarized by system organ class (SOC), preferred term, severity, and

relationship to the study intervention. A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline, with baseline defined as all pre-existing conditions recorded at Visit 1 and any adverse events recorded before the first dose of study intervention (that is, during the interval between Visits 1 and 2 and recorded with the time of onset before the first dose of study intervention). The treatment periods will be used as the postbaseline period for the analysis. Safety analyses will be conducted separately for each treatment period. For events that are gender specific, the denominator and computation of the percentage will include only participants from the given gender.

The number and percentage of participants who experienced TEAEs, TEAEs by maximum severity, deaths, SAEs, TEAEs related to study intervention, discontinuations from the treatment due to an adverse event, and AESIs will be summarized. Treatment-emergent adverse events (all, by maximum severity), SAEs including deaths, and adverse events that lead to treatment discontinuation will be summarized and analyzed by MedDRA SOC and preferred term.

Treatment-related TEAEs (TEAEs related to study intervention) are defined as events that are indicated by the investigator on the eCRF to be related to treatment.

Adverse events of special interest will be identified by a standardized MedDRA query (SMQ) or a Lilly-defined MedDRA preferred term listing.

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (Columbia Lighthouse Project WWW).

Follow-up emergent adverse events, SAEs including deaths, and adverse events that lead to study discontinuation will be summarized. All adverse events, including pre-existing conditions, will be listed by participant, visit, preferred term, treatment group, severity, and relationship to the treatment.

9.4.6. Other Analyses

Sensitivity Analyses

Fisher's exact test may be used as an alternative to logistic regression on the primary endpoint due to the small sample size for this analysis. Other sensitivity analyses will be considered for the secondary endpoints.

9.5. Interim Analyses

The analysis for the primary database lock will be conducted when all participants have either completed the double-blind treatment period (Treatment Period 1) or have discontinued.

Interim analyses at other time points, including time points prior to the primary database lock, may be conducted using safety and/or efficacy data. These interim analyses will be used to support planning activities associated with the development program and to aid in the development of PK/PD modeling. No adjustment of type I error will be performed.

Unblinding details will be specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

Assessments of unblinded interim data will be conducted by an Internal Assessment Committee (IAC) with a limited number of prespecified team members who do not have direct site contact or data entry or data validation responsibilities (see Appendix 10.1, Section 10.1.5). Only the IAC will be authorized to evaluate unblinded interim efficacy and safety analyses.

To minimize bias, the SAP and PK/PD analysis plan will be finalized and approved before any unblinding. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

Study sites will receive information about interim analysis results only if the investigators need to know for the safety of their participants.

The SAP will describe the planned interim analyses in greater detail.

9.6. Data Monitoring Committee (DMC)

Not applicable. An IAC will be used to conduct the interim analysis (see Section 9.5 and Appendix 10.1, Section 10.1.5).

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and
- Applicable laws and regulations.

The protocol, protocol amendments and addenda, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures, and
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 United States Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each principal investigator will sign the separate protocol signature page and send a copy of the signed page to a Lilly representative.

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his or her representative will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary.

Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The sponsor or its representatives must approve the ICFs, including any changes made by the ERBs, before the ICFs are used at the investigative sites.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study. The statement must include the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICFs.

Participants who are rescreened are required to sign a new ICF (see Section 5.4).

Participants must be re-consented to the most current version of the ICF during their participation in the study.

A copy of the ICFs must be provided to the participant or the participant's legally authorized representative and must be kept on file.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his or her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his or her data to be used as described in the informed consent.

The participant must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Internal Assessment Committee (IAC)

In addition to the safety reviews routinely performed by the blinded study team, an IAC will review the efficacy and safety data in an unblinded fashion periodically or on an ad hoc basis during the study and will determine whether any changes (for example, dose reductions or other protocol modifications) should be made.

The IAC reviewing the safety data will be fully independent from the study team and will include, at a minimum, a Lilly medical physician, a statistician, and a representative from the Lilly Global Patient Safety organization. Details about the IAC membership, purpose,

responsibilities, and operation will be described in an IAC charter, which will be approved prior to the first unblinding.

10.1.6. Dissemination of Clinical Study Data

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic (PK) or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www. vivli.org.

10.1.7. Data Quality Assurance

Investigator responsibilities

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (for example, laboratory data).

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This documentation might include laboratory and diagnostic test reports, medical records, and clinical notes.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Data monitoring and management

Monitoring details describing strategy (for example, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data. The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records retention and audits

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment (COA) data (participant-focused outcome instrument) will be collected by the investigative site personnel, via a paper source document and will be transcribed by the investigative site personnel into the EDC system.

Additionally, electronic Clinical Outcome Assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded by the participant and the investigative site personnel, into an instrument (for example, tablet). The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data.

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor's data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global product complaint management system.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The definition of what constitutes source data can be found in Section 10.1.7.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study is open for recruitment of participants.

The sponsor or designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the sponsor.

Site Closure

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided a reasonable cause exists and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include, but are not limited to, these:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator, and
- Discontinuation of further study intervention development.

Premature Termination or Suspension of the Study

The Internal Assessment Committee (IAC) will evaluate unblinded safety data if

- three or more participants experience TEAEs in the same system organ class, and
- these TEAEs are assessed as severe by the investigator and/or meet at least 1 serious criterion and
- these TEAEs are judged as related to blinded study treatment.

Pending the evaluation by the Internal Assessment Committee Study, enrollment and/or further dosing may be stopped, or the dose and/or other study parameters may be modified (Section 9.5 and Section 10.1.5).

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organizations used in the study of the reason for termination or suspension, as specified by the applicable

regulatory requirements. The investigator shall promptly inform the participant and assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

Physicians with a specialty and experience in treatment of patients with hidradenitis suppurativa may participate as investigators.

10.1.12. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable responses that may not be observed until later in the development of LY3041658 or after it becomes commercially available.

The following table lists the maximum retention period for sample types. The retention period begins after the last participant visit for the study.

The maximum retention times may be shorter, if specified in local regulations and/or if ERBs/IRBs impose shorter time limits.

Any samples remaining after the specified retention period will be destroyed.

The sample retention facility will be selected by the sponsor or its designee.

Sample Type	Custodian	Retention Period after Last Participant Visit
Pharmacokinetics	Sponsor or designee	1 year
Long-term storage samples	Sponsor or designee	15 years
Biomarkers (serum, plasma, whole blood for RNA, whole blood for epigenetics)	Sponsor or designee	15 years
Pharmacogenetics sample	Sponsor or designee	15 years
Immunogenicity	Sponsor or designee	15 years

10.2. Appendix 2: Clinical Laboratory Tests

10.2.1. Clinical Laboratory Tests

The clinical laboratory tests listed in the table below will be performed by a central laboratory or by a local laboratory as specified in the table.

Additional tests may be performed at any time during the study as determined necessary by the investigator or as required by local regulations.

Protocol-specific requirements for the inclusion or exclusion of participants are specified in Section 5 of the protocol.

Pregnancy testing is described in the SoA, in Section 8.2.5.1, and in the table below.

Investigators must document their review of each laboratory safety report.

Laboratory test results that could unblind the study will not be reported to investigative sites or other blinded personnel.

	Notes
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (red blood cells [RBC])	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (white blood cells [WBC])	
Absolute count of:	
Neutrophils, segmented	
Neutrophils, juvenile (bands)	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBC and WBC)	

	Notes
Clinical Chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin (TBL)	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	

	Notes
Lipid Panel	Assayed by Lilly-designated laboratory.
Low-density lipoprotein (LDL)	
High-density lipoprotein (HDL)	
Cholesterol (total)	
Triglycerides	

	Notes
Urinalysis	Assayed by Lilly-designated laboratory.
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment	

	Notes
Hormones (females)	
Pregnancy test – serum	Assayed by Lilly-designated laboratory. To be performed only on women of childbearing potential and women with history of tubal ligation.
Pregnancy test – urine	Local testing. To be performed only on women of childbearing potential and women with history of tubal ligation. Result must be negative before dosing at each dosing visit.
Follicle-stimulating hormone (FSH)	Assayed by Lilly-designated laboratory Optional, performed to confirm postmenopausal status.

	Notes
Serology	
Tuberculosis (TB) test:	TB test based on local standard of care (see Section 8.2.6).
QuantiFERON-TB Gold test	Assayed by Lilly-designated laboratory.
T-SPOT.TB	Local testing. Local laboratory must be qualified by local regulations.
Tuberculin skin test (TST)	Local testing. Local laboratory must be qualified by local regulations.
Human immunodeficiency virus (HIV)	Assayed by Lilly-designated laboratory.
Hepatitis C virus (HCV):	
Hepatitis C antibody	Assayed by Lilly-designated laboratory.
HCV RNA	Assayed by Lilly-designated laboratory.
Hepatitis B virus (HBV) testing:	
Hepatitis B core antibody (anti-HBc)	Assayed by Lilly-designated laboratory.
Hepatitis B surface antigen (HBsAg)	Assayed by Lilly-designated laboratory.

	Notes
Biomarkers	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
IL-8	
C reactive protein, high-sensitivity (hs-CRP)	
Total immunoglobins:	
IgA	
IgE	
IgG	
IgM	

	Notes
Pharmacokinetics (PK) Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
LY3041658 concentration	

	Notes
Immunogenicity (ADA) Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-LY3041658 antibodies	
Anti-LY3041658 antibody neutralization	

	Notes
Pharmacogenetics Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Pharmacogenetics sample	

	Notes
Long-Term Stored Samples: Exploratory Biomarker Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Exploratory biomarker samples:	
Serum	
Plasma	
Whole blood RNA	
Whole blood for epigenetics	

10.2.2. Laboratory Tests to be Obtained at Time of a Systemic Hypersensitivity Event

Selected tests should be obtained at the time of a systemic hypersensitivity event, particularly in the presence of generalized urticaria or if anaphylaxis is suspected.

After the participant has been stabilized, obtain a sample within 1 to 2 hours of the event. Samples may be obtained as late as 12 hours after the event.

Record the time at which the sample was collected.

Hypersensitivity Tests [a]

Anti-3041658 antibodies (immunogenicity)	Tryptase *
LY3041658 concentration (pharmacokinetics)	N-methylhistamine
Total immunoglobulins (IgA, IgE, IgG, IgM)	Complements
	Cytokine Panel

[a] Assayed by Lilly-designated laboratory.

* If a tryptase sample is obtained more than 2 hours after the event (that is, within 2 to 12 hours) or is not obtained because more than 12 hours have lapsed since the event, obtain urine for N-methylhistamine (NMH) testing. Note that for tryptase serum samples obtained within 2 to 12 hours of the event, urine NMH testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow-up urine for NMH testing at the next regularly scheduled visit or after 4 weeks, whichever is later.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. NOTE: An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
– Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). – Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or in intensity of the condition. – New conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study. – Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. – Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent; report such overdoses regardless of sequelae. – "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
– Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. The term does not refer to an event which hypothetically might have caused death if the event were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE CRF page.

There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
Not applicable

SAE Reporting via Paper CRF
Facsimile or secure email transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor. Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. Contacts for SAE reporting can be found in in site training documents.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below). If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, consider additional evaluation.

Woman NOT of Childbearing Potential (not WOCBP)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (for example, mullerian agenesis, androgen insensitivity), apply investigator discretion to determining study entry. Determination can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female, defined as a woman meeting one of the following criteria:
  - At least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note.
  - Spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea (for example, oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators [SERMs], or chemotherapy that induced the amenorrhea); additionally, if less than or equal to 50 years of age, has a FSH of ≥40 mIU/mL.
  - At least 40 years of age with an intact uterus, not on hormone therapy, with cessation of menses for at least 1 year, and without an alternative medical cause, AND a FSH of ≥40 mIU/mL.
  - At least 55 years of age, not on hormone therapy, having at least 12 months of spontaneous amenorrhea.
  - At least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

10.4.2. Contraception

Females

Women of childbearing potential

- Women of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males. Periodic abstinence (for example, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.
- Otherwise, women of childbearing potential participating must agree to use 2 forms of effective contraception, where at least 1 form is highly effective (less than 1% failure rate), for the entirety of the study. Abstinence or contraception must continue following completion of study drug administration for 12 weeks.
    - Women of childbearing potential participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.
    - Two forms of effective contraception, where at least 1 form is highly effective, (such as combination oral contraceptives, implanted contraceptives or intrauterine devices) will be used. Effective contraception (such as male or female condoms with spermicide, diaphragms with spermicide or cervical sponges) may be used as the second therapy. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide). It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

Women not of childbearing potential (not WOCBP)

Women who are not WOCBP may participate in the study if they meet all study entry criteria. For such women, there are no conception requirements.

Males

- Men, regardless of their fertility status, with nonpregnant WOCBP partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as 1 additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges) for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, that is, 90 days following the last dose.
    - Men and their partners may choose to use a double–barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a

double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined).

- Periodic abstinence (for example, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

- Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure in WOCBP (90 days following the last dose).
- Men should refrain from sperm donation for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, that is, 90 days following the last dose.
- Men who are in exclusively same sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

10.4.3. Collection of Pregnancy Information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an adverse event (AE) or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

10.5. Appendix 5: Liver Safety: Hepatic Monitoring Tests

Sampling in the case of a treatment-emergent hepatic abnormality

Samples for selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required during follow-up with participants in consultation with the clinical research physician of the sponsor or sponsor's designee.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalised ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by sponsor-designated or local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

10.6. Appendix 6: Examples of Infections That May Be Considered Opportunistic in the Setting of Biologic Therapy

The following table lists examples of infections that may be considered opportunistic in the setting of biologic therapy (adapted from Winthrop et al. [2015]). This table is provided to aid the investigator in recognizing such infections. This list is not exhaustive. Infections will be categorized by Lilly as opportunistic according to *Opportunistic Infections and Biologic Therapies in Immune-Mediated Inflammatory Diseases: Consensus Recommendations for Infection Reporting during Clinical Trials and Postmarketing Surveillance* by Winthrop et al. (2015).

Examples of Infections That May Be Considered Opportunistic in the Setting of Biologic Therapy

Bacterial	
	Bartonellosis (disseminated disease only)
	Campylobacteriosis (invasive disease only)
	Legionellosis
	Listeriosis (invasive disease only)
	Nocardiosis
	Tuberculosis
	Non-tuberculous mycobacterial disease
	Salmonellosis (invasive disease only)
	Shigellosis (invasive disease only)
	Vibriosis (invasive disease due to *Vibrio vulnificus*)
Viral	
	BK virus disease including polyomavirus-associated nephropathy
	Cytomegalovirus disease
	Hepatitis B virus reactivation
	Hepatitis C virus progression
	Herpes simplex (invasive disease only)
	Herpes zoster (any form)
	Post-transplant lymphoproliferative disorder (Epstein-Barr virus)
	Progressive multifocal leukoencephalopathy (PML), John Cunningham (JC) virus
Fungal	
	Aspergillosis (invasive disease only)
	Blastomycosis
	Candidiasis (invasive disease or oropharyngeal, esophageal. Not isolated lingual.)
	Coccidioidomycosis
	Cryptococcosis
	Histoplasmosis
	Paracoccidioides infections
	Penicilliosis
	Pneumocystosis
	Sporotrichosis
	Other invasive molds: Mucormycosis (zygomycosis) (*Rhizopus*, *Mucor,* and *Lichtheimia*), *Scedosporium*/*Pseudallescheria boydii*, *Fusarium*
Parasitic	
	Leishmaniasis (visceral only)
	Strongyloidosis (hyperinfection syndrome or disseminated disease)
	Microsporidiosis
	Toxoplasmosis
	Trypanosoma cruzi infection (Chagas' disease progression) (disseminated disease only)
	Cryptosporidiosis (chronic disease only)

Source: Adapted from Winthrop et al. (2015).

10.7. Appendix 7: Abbreviations

Term	Definition
A	abscesses, when used in the context of lesion counts
ADA	anti-drug antibody
ASAS	Assessment of SpondyloArthritis International Society
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AN count	total abscess and inflammatory nodule count
ANC	absolute neutrophil count
anti-HBc	antibody to hepatitis B core antigen
AST	aspartate aminotransferase
blinding	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CBD	cannabidiol
CFR	United States Code of Federal Regulations
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
C-SSRS	Columbia Suicide-Severity Rating Scale
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXR	chest x-ray
DF	draining fistulas, when used in the context of lesion counts
DLQI	Dermatology Life Quality Index

DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCOA/COA	electronic Clinical Outcome Assessment/Clinical Outcome Assessment
eCRF/CRF	electronic case report form/case report form
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethical Review Board (see IRB)
ETV	early termination visit
F	nondraining fistulas, when used in the context of lesion counts
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HiSCR	Hidradenitis Suppurativa Clinical Response, defined as at least a 50% reduction in the total abscess and inflammatory nodule count (AN count) with no increase in abscess count and no increase in draining fistulae count relative to baseline
HIV	human immunodeficiency virus
HS	hidradenitis suppurativa
hs-CRP	C reactive protein, high-sensitivity
IAC	Internal Assessment Committee
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee (see IRB)
Ig	immunoglobulin

IGRA	interferon gamma release assay
IHS4	International Hidradenitis Suppurativa Severity Score System
IL	interleukin
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board (IRB), also called Independent Ethics Committee (IEC) or Ethical Review Board (ERB)
mITT	modified intent-to-treat
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive web-response system
LTBI	latent tuberculosis infection
mSS	modified Sartorius Score
N	inflammatory nodules, when used in the context of lesion counts
NOAEL	no-observed-adverse-effect level
NONMEM	nonlinear mixed effects modeling
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
PA	posterior–anterior

participant	Equivalent to Clinical Data Interchange Standards Consortium (CDISC) term "subject," meaning an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control. In this protocol, the term "participant" is used to indicate an individual who participates in a clinical trial, either as a recipient of an investigational medicinal product or as a control. This usage reflects preferences indicated by patient advocates to more accurately reflect the role of people who take part in clinical trials.
PD	pharmacodynamics
PK	pharmacokinetics
PK/PD	pharmacokinetics/pharmacodynamics
PPD	purified protein derivative
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
Q2W	every 2 weeks
QTc	corrected QT interval
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	Schedule of Activities
study drug	See "study intervention"
study intervention	Any investigational intervention, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol
TB	tuberculosis
TBL	total bilirubin level
TE	treatment emergent
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TST	tuberculin skin test
ULN	upper limit of normal

USA	United States of America; also United States
WBC	white blood cell
WOCBP	women of childbearing potential (see Appendix 10.4, Section 10.4.1.)
xN	non-inflammatory nodules, when used in the context of lesion counts

11. References

A study to evaluate the efficacy, safety, and tolerability of guselkumab for the treatment of participants with moderate to severe hidradenitis suppurativa (HS) (NOVA). ClinicalTrials.gov website. https://clinicaltrials.gov/ ct2/show/NCT03628924. Updated January 22, 2020. Accessed February 13, 2020.

A study of efficacy and safety of two secukinumab dose regimens in subjects with moderate to severe hidradenitis suppurativa (HS) (SUNRISE). ClinicalTrials.gov website. https://clinicaltrials.gov/ ct2/show/NCT03713632. Updated February 6, 2020. Accessed February 13, 2020.

A study of efficacy and safety of two secukinumab dose regimens in subjects with moderate to severe hidradenitis suppurativa (HS). (SUNSHINE). ClinicalTrials.gov website. https://clinicaltrials.gov/ ct2/show/NCT03713619. Updated November 19, 2019. Accessed February 13, 2020

A study to evaluate the efficacy and safety of bimekizumab in study participants with moderate to severe hidradenitis suppurativa (BE HEARD I). ClinicalTrials.gov website. https://clinicaltrials.gov/ ct2/show/ NCT04242446. Updated January 27, 2020. Accessed February 13, 2020.

A study to test the efficacy and safety of bimekizumab in study participants with moderate to severe hidradenitis suppurativa (BE HEARD II). ClinicalTrials.gov website. https://clinicaltrials.gov/ ct2/show/ NCT04242498. Updated January 27, 2020. Accessed February 13, 2020.

Basra MK, Salek MS, Camilleri L, et al. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology*. 2015;230(1):27-33. https://doi.org/ 10.1159/000365390

Columbia Lighthouse Project. The Columbia Protocol for Research. Columbia-Suicide Severity Rating Scale Scoring and Data Analysis Guide. Version 2.0. Available at: http:// cssrs.columbia.edu/wp-content/uploads/ScoringandDataAnalysisGuide-for-Clinical-Trials-1.pdf. Accessed 30 January 2019.

Hongbo Y, Thomas CL, Harrison MA, et al. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? *J Invest Dermatol*. 2005;125(4):659-664. https://doi.org/ 10.1111/j.0022-202X.2005.23621.x

Hurley H. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa, and familial benign pemphigus: surgical approach. In: Roenigk RK, Roenigk HH, editors. *Dermatologic surgery: Principles and practice*. New York: Marcel Dekker; 1989:p 729-739.

Kimball AB, Jemec GB, Yang M, et al. Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. *Br J Dermatol*. 2014;171(6):1434-1442. https://doi.org/ 10.1111/bjd.13270

Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med*. 2016a;375(5):422-434. https://doi.org/ 10.1056/NEJMoa1504370

Kimball AB, Sobell JM, Zouboulis CC, et al. HiSCR (Hidradenitis Suppurativa Clinical Response): a novel clinical endpoint to evaluate therapeutic outcomes in patients with hidradenitis suppurativa from the placebo-controlled portion of a phase 2 adalimumab study. *J Eur Acad Dermatol Venereol*. 2016b;30(6):989-994. https://doi.org/ 10.1111/jdv.13216

Kouris A, Platsidaki E, Christodoulou C, et al. Quality of life and psychosocial implications in patients with hidradenitis suppurativa. *Dermatology.* 2016;232(6):687-691. https://doi.org/ 10.1159/000453355.

Sartorius K, Emtestam L, Jemec GB, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. *Br J Dermatol.* 2009;161(4):831-839. https://doi.org/ 10.1111/j.1365-2133.2009.09198.x

Sieper J, van der Heijde D, Landewé R, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of Spondyloarthritis International Society (ASAS). *Ann Rheum Dis*. 2009;68(6):784-788. https://doi.org/ 10.1136/ard.2008.101501

Vekic DA, Cains GD. Hidradenitis suppurativa - management, comorbidities and monitoring. *Aust Fam Physician.* 2017;46(8):584-588.

Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. *Ann Rheum Dis*. 2015;74(12):2107-2116. https://doi.org/ 10.1136/annrheumdis-2015-207841

Zouboulis CC. Hidradenitis suppurativa/acne inversa: the clinical challenge [abstract]. *Experimental Dermatology*. 2006;15(6):478. Abstract. https://doi.org/ 10.1111/j.0906-6705.2006.0436a.x

Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol*. 2015;29(4):619-644. https://doi.org/ 10.1111/jdv.12966

Zouboulis CC, Tzellos T, Kyrgidis A, et al. Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity. *Br J Dermatol.*. 2017;177(5):1401–1409. https://doi.org/ 10.1111/bjd.15748

Leo Document ID = 4b826219-07d1-404d-9ab5-2e69ee79dc31

Approver: PPD

Approval Date & Time: 12-Aug-2021 16:14:29 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 13-Aug-2021 13:06:25 GMT

Signature meaning: Approved